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

Iadademstat and Gilteritinib for the Treatment of FLT3-Mutated Relapsed/Refractory Acute Myeloid Leukemia: The Frida Study

Amir T. Fathi, MD[1], *Theodore P Braun, MD PhD*[2], *Alexander Joseph Ambinder, MD MPH*[3], *Gautam Borthakur, MD*[4], *Robert L. Redner, MD*[5], *Mabel Arevalo*[6], *Sonia Gutierrez*[6], *Ana Limon, PhD*[7], *Douglas V. Faller, MDPhD*[7]

[1] Division of Hematology/Oncology, Massachusetts General Hospital, Boston, MA
[2] Division of Hematology & Medical Oncology, Oregon Health & Science University, Portland, OR
[3] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
[4] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[5] University of Pittsburgh Medical Center, Pittsburgh, PA
[6] Oryzon Genomics, Cornella de Llobregat, Spain
[7] Oryzon Genomics, Boston, MA

Background: Frontline and relapsed /refractory (R/R) acute myeloid leukemia (AML) patients carrying fms-related tyrosine kinase 3 [FLT3]-mutations (FLT3 mut+) benefit from FLT3 inhibitors (FLT3i) that have emerged as active therapeutic agents for this subset of AML encompassing up to 30-40% of all AML cases. The FLT3i gilteritinib, as monotherapy for R/R AML pts, has improved outcomes but the duration of remission achieved is transient and often brief. The Phase 3 randomized ADMIRAL trial of gilteritinib demonstrated a 20% CR rate and 2.8 months event-free-survival (EFS) (Perl, et al., NEJM 2019). The development of new targeted agents which synergize with FLT3 inhibitors, and ideally also inhibit the emergence of resistance, is therefore a major medical need in AML.

Iadademstat (iada/ORY-1001) is a specific, oral, potent, covalent inhibitor of the epigenetic Lysine-Specific Demethylase 1 (LSD1/KDMA1) enzyme. Epigenetic dysregulation is a hallmark of AML. Up to 70% of recurring mutations in AML patients target epigenetic regulators of gene expression, resulting in myeloid differentiation blockade and enhanced leukemic stem cell renewal, underscoring the potential of epigenetic therapies to change the natural history of the disease.

Preclinically, iada produces striking synergy with FLT3is, particularly gilteritinib in FLT3 wild-type and FLT3 mut+ AML cells and in derived cell lines resistant to venetoclax, azacitidine and other FLT3is (Sacilotto et al., 2022 Eur J. of Cancer 174S1). The novel MOAs generating this synergy in combinations include activation of a pro-differentiating epigenetic transcriptional program with simultaneous suppression of MYC-driven target genes (Yashar, et al. 2023, Mol. Cancer Res).

The recently completed Phase 2 study of iada in combination with azacitidine (ALICE) produced a high rate of composite remission, including complete remission (CR) and CR with incomplete count recovery (CRi) (mostly MRD negative), as well as durable responses, in treatment naïve, unfit AML patients (pts), without exacerbating the toxicity profile of azacitidine (Salamero et al., 2022, Blood S1).

The FRIDA study (NCT05546580) aims to establish the safety, tolerability, and the recommended phase 2 dose (RP2D) of the combination of iada plus gilteritinib in FLT3 mut+ R/R AML.

Methods: Adult pts with body weight ≥50 Kg and ECOG 0-2, with FLT3 mut+ R/R AML, after no more than 2 prior lines of therapy, are enrolling. Certain patients with prior exposure to FLT3is including gilteritinib may be eligible. Up to 18 pts, in a 3+3 escalation phase, will receive iada at doses of 75 to 150 ug, orally, in 5 days ON - 2 days OFF schedule, with continuous gilteritinib, at 120 mg/day orally. In the expansion phase, up to 14 pts at the selected safe and pharmacologically active dose/s (determined based on all available data from escalation pts including PK, target engagement (TE), safety, tolerability, and emerging activity) will be enrolled.

Primary endpoints of the study are safety and RP2D determination, based on the same 5 criteria outlined above. Bayesian posterior probability efficacy monitoring will be performed periodically for each dose cohort in the expansion phase. Bayesian efficacy futility and early stopping boundary will be applied during the monitoring. Posterior probability criterion (Prob (CR>0.3) ≥ 0.60) at the end of the study will warrant additional development. The safety of the combination treatment will also be continuously evaluated during expansion following a Bayesian design stopping rule.Secondary endpoints include overall survival,

EFS, CR, CR/CR with partial hematologic recovery (CRh), overall response rates, time to response, duration of response, and transfusion rate. Exploratory endpoints include measurable residual disease and gene mutational analysis.
At the time of the submission, FRIDA is enrolling a second dose level cohort in escalation phase and plans to have the 15 sites open to accrual in the US by the end of 2023. Additional sites will be added for a subsequent randomized controlled double-blinded FRIDA 2 study to assess the efficacy of the iada and gilteritinib combination in R/R FLT3 mut+ AML.

Disclosures Fathi: *Menarini:* Consultancy; *Immunogen:* Consultancy; *Ipsen:* Consultancy; *Kite:* Consultancy; *Novartis:* Consultancy; *Orum:* Consultancy; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Mablytics:* Consultancy; *Celgene:* Consultancy, Research Funding; *Enclear:* Consultancy; *Daiichi Sankyo:* Consultancy; *Forma:* Consultancy; *Genentech:* Consultancy; *PureTech:* Consultancy; *Pfizer:* Consultancy; *Autolus:* Consultancy; *Astellas:* Consultancy; *Amgen:* Consultancy; *Agios:* Consultancy; *AbbVie:* Consultancy, Research Funding; *Gilead:* Consultancy; *Remix:* Consultancy; *Rigel:* Consultancy; *Servier:* Consultancy, Research Funding; *Takeda:* Consultancy. **Braun:** *Novartis:* Consultancy; *Gilead Sciences:* Research Funding; *Blueprint Medicines:* Consultancy, Research Funding; *AstraZeneca:* Research Funding; *Oryzon Genomics:* Other: Institutional PI (FRIDA trial). **Borthakur:** *Astex Pharmaceuticals, Ryvu, PTC Therapeutics:* Research Funding; *Pacylex, Novartis, Cytomx, Bio Ascend::* Membership on an entity's Board of Directors or advisory committees; *Catamaran Bio, Abbvie, PPD Development, Protagonist Therapeutics, Janssen:* Consultancy. **Arevalo:** *Oryzon Genomics:* Current Employment. **Gutierrez:** *Oryzon Genomics:* Current Employment. **Limon:** *Oryzon Genomics:* Current Employment, Current equity holder in publicly-traded company; *Viracta:* Current equity holder in publicly-traded company; *Tango Therapeutics:* Current Employment, Current equity holder in publicly-traded company; *BMS:* Current equity holder in publicly-traded company. **Faller:** *Viracta Therapeutics:* Current Employment, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties; *Phoenicia Biosciences:* Current Employment, Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Oryzon Genomics:* Current Employment, Current equity holder in publicly-traded company; *Briacell:* Consultancy, Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Cytea:* Consultancy, Current equity holder in private company; *Takeda pharmaceuticals:* Current equity holder in publicly-traded company, Ended employment in the past 24 months; *Faller Williams LLC:* Current equity holder in private company, Patents & Royalties; *Molecular Partners:* Consultancy; *Wuxi Inc:* Consultancy.

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