ORYZON announces journal publication of final Phase IIa ALICE results with iadademstat in *The Lancet Haematology*

- **The Phase IIa study ALICE evaluated the combination of iadademstat plus azacitidine in newly diagnosed, unfit patients with acute myeloid leukemia (AML)**
- **The combination showed substantial antileukemic activity with deep responses and a manageable safety profile, including in patients with high-risk prognostic factors**
- **Iadademstat continues to be studied in 1L unfit AML patients through an investigator-initiated study with Oregon Health & Science University (OHSU)**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, June 3rd, 2024 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company leveraging epigenetics to develop therapies in diseases with strong unmet medical need, announced today that the final results of the Phase IIa ALICE study evaluating iadademstat in combination with azacitidine in unfit patients with newly diagnosed acute myeloid leukemia (AML) were published online in *The Lancet Haematology* . A summary of the final data from this study had been previously released in an oral presentation at the 2022 American Society for Hematology (ASH) annual meeting, where it was selected as one of the 25 most relevant communications in AML.

This notable publication is a continuation of Oryzon's previous pioneering research featured in the *Journal of Clinical Oncology* (First-in-Human study in AML with iadademstat) and *Cancer Cell* (Characterization of iadademstat as a potent and selective LSD1 inhibitor), cementing the company's position at the forefront of epigenetics in oncology and LSD1 innovation.

Dr. Carlos Buesa, Oryzon's CEO, stated, "We are thrilled to publish these groundbreaking results in one of the most prestigious journals in clinical oncology. Our study demonstrates that targeting LSD1 is a completely novel anti-leukemic mechanism of action in AML, potentially offering a new therapeutic approach, especially for patients with hard-to-treat forms of the disease such as myelomonocytic leukemias, DNMTs mutations, or TP53 mutations. These patients currently respond poorly to available treatments and may benefit from the innovative treatment option of iadademstat. We want to reiterate our gratitude to the patients, their families and the researchers involved in this study."

Summary of the main results reported in the publication

- The combination of iadademstat with azacitidine induced a high proportion of responses, with 22 (82%) of 27 patients in the efficacy analysis set having an objective response. Notably, 52% of patients had either a complete remission (CR) or complete remission with incomplete hematological recovery (CRi) in the ALICE trial. For comparison, the percentage of patients who experienced a CR/CRi in the intention-to-treat azacitidine populations was 28% in the acute myeloid leukaemia-001 trial, 28% in the VIALE A trial, and 27% in the Monarch trial.

- Most of the responses occurred rapidly (87% by the second assessment) and 36% lasted 12 months or longer. At database lock (1 year after the last patient was enrolled), nine patients were alive and as of February, 2024, five patients remain alive, with three continuing treatment (and in complete remission) under compassionate use after four years.

- The CR/CRi responses in ALICE were generally deep, as determined by the high rate of measurable residual disease (MRD) negativity (91% in the evaluable samples), which is associated with improved survival.

- Remarkably, responses were seen across the entire adverse prognostic mutational landscape. Of note are the responses in specific subgroups:
    - Three patients with M5 AML (a population primary refractory to venetoclax and azacitidine) had CR/CRi with iadademstat plus azacitidine, with 100% measurable residual disease negativity.
    - In patients with AML with TP53 mutations in combination with a complex karyotype or high variant allele frequency, or both, CR/CRi was reached in 63%, with a duration of response of 7.9 months and a median overall survival of 10 months.
    - Responses in leukemias harboring other poorer-prognosis mutations were also encouraging. All seven patients harboring a mutation or mutations in the RAS pathway responded, with a median overall survival of 467 days. Patients harboring mutations in DNM3TA (n=7), NPM1 (n=4), and RUNX (n=3) had 100% response rates, mostly CR or CRi.

A temporary link to access the online publication for free can be found here.

As a continuation of ALICE, Oryzon is further expanding the clinical development of iadademstat in 1L unfit AML through an Investigator-initiated study (IIS) led by Oregon Health & Science University (OHSU). This trial is a Phase Ib dose-finding study to evaluate iadademstat in combination with the SoC, venetoclax and azacitidine, in first-line AML patients and is expected to begin enrolling patients in the coming weeks.

Iadademstat is currently being evaluated also in combination with gilteritinib in relapsed/refractory AML patients harboring a FLT3 mutation in the FRIDA study, an open-label, multicenter Phase Ib trial being conducted in the US and which plans to accrue up to approximately 45 patients. The first two cohorts have been completed (thirteen patients), and the combination was safe and showed strong antileukemic activity. Following the FDA's new OPTIMUS doctrine, the company continues to explore the minimal dose with clinical activity, and a third cohort has been started and is recruiting. Preliminary results from this trial will be presented at the upcoming European Hematology Association (EHA) 2024 congress in June.

In addition, in neuroendocrine tumors, in the context of the CRADA agreement between Oryzon and the NIH, the NCI is sponsoring a randomized Phase I/II trial in 1L extensive disease small cell lung cancer combining iadademstat with immune checkpoint inhibitors. The IND for this trial was recently approved by the FDA.

About Oryzon

Founded in 2000 in Barcelona, Spain, Oryzon (ISIN Code: ES0167733015) is a clinical stage biopharmaceutical company and the European leader in epigenetics, with a strong focus on personalized medicine in CNS disorders and oncology. Oryzon's team is composed of highly qualified professionals from the pharma industry located in Barcelona, Boston, and San Diego. Oryzon has an advanced clinical portfolio with two LSD1 inhibitors, vafidemstat in CNS and iadademstat in oncology, in several Phase II clinical trials. The company has other pipeline assets directed against other epigenetic targets like HDAC-6, where ORY-4001 has been nominated as clinical candidate for the treatment of certain neurological disorders such as CMT and ALS. In addition, Oryzon has a strong platform for biomarker identification and target validation for a variety of malignant and neurological diseases. For more information, visit www.oryzon.com

About Iadademstat

Iadademstat (ORY-1001) is a small oral molecule, which acts as a highly selective inhibitor of the epigenetic enzyme LSD1 and has a powerful differentiating effect in hematologic cancers (see Maes et al., Cancer Cell 2018 Mar 12; 33 (3): 495-511.e12.doi: 10.1016 / j.ccell.2018.02.002.). A FiM Phase I/IIa clinical trial with iadademstat in R/R AML patients demonstrated the safety and good tolerability of the drug and preliminary signs of antileukemic activity, including a CRi (see Salamero et al, J Clin Oncol, 2020, 38(36): 4260-4273. doi: 10.1200/JCO.19.03250). Iadademstat has shown encouraging safety and efficacy data in combination with azacitidine in a Phase IIa trial in elder 1L AML patients (ALICE trial) (see Salamero et al., ASH 2022 oral presentation). Iadademstat is currently being evaluated in combination with gilteritinib in the ongoing Phase Ib FRIDA trial in patients with relapsed/refractory AML with FLT3 mutations. Beyond hematological cancers, the inhibition of LSD1 has been proposed as a valid therapeutic approach in some solid tumors such as small cell lung cancer (SCLC), neuroendocrine tumors (NET), medulloblastoma and others. In a Phase IIa trial in combination with platinum/etoposide in second line ED-SCLC patients (CLEPSIDRA trial), preliminary activity and safety results have been reported (see Navarro et al., ESMO 2018 poster). Iadademstat is being evaluated in a collaborative Phase II basket study with the Fox Chase Cancer Center (FCCC) in combination with paclitaxel in R/R neuroendocrine carcinomas, and the company is preparing a new trial in combination with immune checkpoint inhibitors (ICI) in SCLC. Oryzon has entered into a Cooperative Research and Development Agreement (CRADA) with the U.S. National Cancer Institute (NCI) to collaborate on potential further clinical development of iadademstat in different types of solid and hematological cancers; a first trial in combination with ICI in SCLC has recently received FDA IND approval. In total iadademstat has been dosed so far to more than 130 cancer patients in four clinical trials. Iadademstat has orphan drug designation for SCLC in the US and for AML in the US and EU.

FORWARD-LOOKING STATEMENTS

This communication contains, or may contain, forward-looking information and statements about Oryzon, including financial projections and estimates and their underlying assumptions, statements regarding plans, objectives, and expectations with respect to future operations, capital expenditures, synergies, products and services, and statements regarding future performance. Forward-looking statements are statements that are not historical facts and are generally identified by the words "expects," "anticipates," "believes," "intends," "estimates" and similar expressions. Although Oryzon believes that the expectations reflected in such forward-looking statements are reasonable, investors and holders of Oryzon shares are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Oryzon that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include those discussed or identified in the documents sent by Oryzon to the Spanish *Comisión Nacional del Mercado de Valores* (CNMV), which are accessible to the public. Forward-looking statements are not guarantees of future performance and have not been reviewed by the auditors of Oryzon. You are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date they were made. All subsequent oral or written forward-looking statements attributable to Oryzon or any of its members, directors, officers, employees, or any persons acting on its behalf are expressly qualified in their entirety by the cautionary statement above. All forward-looking statements included herein are based on information available to Oryzon on the date hereof. Except as required by applicable law, Oryzon does not undertake any obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events, or otherwise. This press release is not an offer of securities for sale in the United States or any other jurisdiction. Oryzon's securities may not be offered or sold in the United States absent registration or an exemption from registration. Any public offering of Oryzon's securities to be made in the United States will be made by means of a prospectus that may be obtained from Oryzon or the selling security holder, as applicable, that will contain detailed information about Oryzon and management, as well as financial statements.

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