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Rigel Announces Second REZLIDHIA® (Olutasidenib) Publication in Blood Advances

- Review article examines the preclinical and clinical development, and the role of olutasidenib in the m*IDH1* AML treatment landscape.
- Authors conclude, "The approval of olutasidenib is a critical addition to the m*IDH1* AML treatment landscape with encouragingly durable responses."

SOUTH SAN FRANCISCO, Calif., June 6, 2023 /PRNewswire/ -- Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL) today announced an expert review article in *Blood Advances* examining the development path and positioning of REZLIDHIA® (olutasidenib), a potent, selective, oral, small-molecule inhibitor of mutant isocitrate dehydrogenase-1 (m*IDH1*)[1], in the m*IDH1* relapsed/refractory (R/R) acute myeloid leukemia (AML) treatment landscape.

"The compelling safety and efficacy results observed in REZLIDHIA trials to date, marked by encouragingly durable responses, represent an important advance for m*IDH1* R/R AML patients and treating physicians," said Justin Watts, M.D., Lead Author and Associate Professor of Medicine, Division of Hematology, Chief, Leukemia Section at the University of Miami Health System. "These data are particularly supportive of the use of REZLIDHIA in m*IDH1* R/R AML patients who have failed intensive chemotherapy or venetoclax plus HMA combination therapy. The results validate ongoing studies evaluating olutasidenib in frontline and R/R settings as a monotherapy and in combination with azacitidine with or without prior exposure to HMA or IDH1 inhibitor."

"We are pleased with the growing body of evidence and thought leader support for REZLIDHIA as a differentiated and potentially market-leading therapy for m*IDH1* R/R AML patients," said Raul Rodriguez, Rigel's president and CEO. "We remain committed to delivering this important treatment option to m*IDH1* R/R AML patients and look forward to data from the ongoing studies of REZLIDHIA in broader m*IDH1* AML treatment settings."

Key points from the paper are summarized below:

- REZLIDHIA demonstrated highly durable remission rates, representing a critical addition to the m*IDH1* AML treatment landscape
- The available data support the use of REZLIDHIA as monotherapy in R/R AML patients who have failed intensive chemotherapy or venetoclax plus HMA combination

therapy
- The authors state that the choice of which IDH1 inhibitor to use first in these patients is not yet clear, although given the available data REZLIDHIA is recommended in venetoclax plus HMA failures
    - Among the 12 patients with prior exposure to venetoclax, the ORR was 50% with four patients achieving CR/CRh (33%; 95% CI, 9.9–65.1) and two patients had CRi
- Ongoing studies (NCT02719574) could clarify the role of REZLIDHIA in treatment naïve m*IDH1* AML (including when given in combination with azacitidine) and in R/R m*IDH1* AML with prior IDH1 inhibitor exposure. Further studies assessing maintenance, triplet therapy, and sequencing with venetoclax and azacitidine are being considered.

The paper, titled "Olutasidenib: from Bench to Bedside," was published online in*Blood Advances* and can be accessed here.

Rigel announced a peer-reviewed publication of data in*Blood Advances* in February 2023, which summarizes clinical results from the Phase 2 registrational trial of REZLIDHIA in patients with m*IDH1* R/R AML.

On December 1, 2022, the U.S. Food and Drug Administration (FDA) approved REZLIDHIA (olutasidenib) capsules for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA-approved test. REZLIDHIA became commercially available in the U.S. on December 22, 2022. REZLIDHIA was added to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for acute myeloid leukemia (AML) on January 13, 2023 as a recommended targeted therapy for adult patients with R/R AML with isocitrate dehydrogenase-1 (IDH1) mutation.

About AML

Acute myeloid leukemia (AML) is a rapidly progressing cancer of the blood and bone marrow that affects myeloid cells, which normally develop into various types of mature blood cells. AML occurs primarily in adults and accounts for about 1 percent of all adult cancers. The American Cancer Society estimates that in the United States alone, there will be about 20,380 new cases, most in adults, in 2023.[2]

Relapsed AML affects about half of all patients who, following treatment and remission, experience a return of leukemia cells in the bone marrow.[3] Refractory AML, which affects between 10 and 40 percent of newly diagnosed patients, occurs when a patient fails to achieve remission even after intensive treatment.[4] Quality of life declines for patients with each successive line of treatment for AML, and well-tolerated treatments in relapsed or refractory disease remain an unmet need.

About REZLIDHIA®

INDICATION

REZLIDHIA is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME
Differentiation syndrome, which can be fatal, can occur with REZLIDHIA treatment. Symptoms may include dyspnea, pulmonary infiltrates/pleuropericardial effusion, kidney injury, hypotension, fever, and weight gain. If differentiation syndrome is suspected, withhold REZLIDHIA and initiate treatment with corticosteroids and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome

REZLIDHIA can cause differentiation syndrome. In the clinical trial ofREZLIDHIA in patients with relapsed or refractory AML, differentiation syndrome occurred in 16% of patients, with grade 3 or 4 differentiation syndrome occurring in 8% of patients treated, and fatalities in 1% of patients. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal. Symptoms of differentiation syndrome in patients treated with REZLIDHIA included leukocytosis, dyspnea, pulmonary infiltrates/pleuropericardial effusion, kidney injury, fever, edema, pyrexia, and weight gain. Of the 25 patients who experienced differentiation syndrome, 19 (76%) recovered after treatment or after dose interruption of REZLIDHIA. Differentiation syndrome occurred as early as 1 day and up to 18 months after REZLIDHIA initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, temporarily withhold REZLIDHIA and initiate systemic corticosteroids (e.g., dexamethasone 10 mg IV every 12 hours) for a minimum of 3 days and until resolution of signs and symptoms. If concomitant leukocytosis is observed, initiate treatment with hydroxyurea, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms. Differentiation syndrome may recur with premature discontinuation of corticosteroids and/or hydroxyurea treatment. Institute supportive measures and hemodynamic monitoring until improvement; withhold dose of REZLIDHIA and consider dose reduction based on recurrence.

Hepatotoxicity

REZLIDHIA can cause hepatotoxicity, presenting as increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood alkaline phosphatase, and/or elevated bilirubin. Of 153 patients with relapsed or refractory AML who received REZLIDHIA, hepatotoxicity occurred in 23% of patients; 13% experienced grade 3 or 4 hepatotoxicity. One patient treated with REZLIDHIA in combination with azacitidine in the clinical trial, a combination for which REZLIDHIA is not indicated, died from complications of drug-induced liver injury. The median time to onset of hepatotoxicity in patients with relapsed or refractory AML treated with REZLIDHIA was 1.2 months (range: 1 day to 17.5 months) after REZLIDHIA initiation, and the median time to resolution was 12 days (range: 1 day to 17 months). The most common hepatotoxicities were elevations of ALT, AST, blood alkaline phosphatase, and blood bilirubin.

Monitor patients frequently for clinical symptoms of hepatic dysfunction such as fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Obtain baseline liver function tests prior to initiation of REZLIDHIA, at least once weekly for the first two months, once every other week for the third month, once in the fourth month, and once every other month for the duration of therapy. If hepatic dysfunction occurs, withhold, reduce, or permanently discontinue REZLIDHIA based on recurrence/severity.

ADVERSE REACTIONS
The most common (≥20%) adverse reactions, including laboratory abnormalities, were aspartate aminotransferase increased, alanine aminotransferase increased, potassium decreased, sodium decreased, alkaline phosphatase increased, nausea, creatinine increased, fatigue/malaise, arthralgia, constipation, lymphocytes increased, bilirubin increased, leukocytosis, uric acid increased, dyspnea, pyrexia, rash, lipase increased, mucositis, diarrhea and transaminitis.

DRUG INTERACTIONS

- Avoid concomitant use of REZLIDHIA with strong or moderate CYP3A inducers.
- Avoid concomitant use of REZLIDHIA with sensitive CYP3A substrates unless otherwise instructed in the substrates prescribing information. If concomitant use is unavoidable, monitor patients for loss of therapeutic effect of these drugs.

LACTATION
Advise women not to breastfeed during treatment with REZLIDHIA and for 2 weeks after the last dose.

GERIATRIC USE
No overall differences in effectiveness were observed between patients 65 years and older and younger patients. Compared to patients younger than 65 years of age, an increase in incidence of hepatotoxicity and hypertension was observed in patients ≥65 years of age.

HEPATIC IMPAIRMENT
In patients with mild or moderate hepatic impairment, closely monitor for increased probability of differentiation syndrome.

Click here for Full Prescribing Information, including Boxed WARNING.

To report side effects of prescription drugs to the FDA, visitwww.fda.gov/medwatch or call 1-800-FDA-1088 (800-332-1088).

REZLIDHIA is a registered trademark of Rigel Pharmaceuticals, Inc.

About Rigel
Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL) is a biotechnology company dedicated to discovering, developing and providing novel small molecule drugs that significantly improve the lives of patients with hematologic disorders, cancer, and rare immune diseases. Founded in 1996, Rigel is based in South San Francisco, California. For more information on Rigel, the Company's marketed products and pipeline of potential products, visit www.rigel.com.

1. de Botton S, et al. Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory *IDH1*-mutated AML. *Blood Advances*. February 1, 2023.
   doi: https://doi.org/10.1182/bloodadvances.2022009411
2. The American Cancer Society. Key Statistics for Acute Myeloid Leukemia (AML). Revised January 12, 2023. Accessed Feb. 15, 2023: https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html

3. Leukaemia Care. Relapse in Acute Myeloid Leukaemia (AML). Version 3. Reviewed October 2021. Accessed Dec 2, 2021: https://media.leukaemiacare.org.uk/wp-content/uploads/Relapse-in-Acute-Myeloid-Leukaemia-AML-Web-Version.pdf
4. Thol F, Schlenk RF, Heuser M, Ganser A. How I treat refractory and early relapsed acute myeloid leukemia. *Blood* (2015) 126 (3): 319-27. doi: https://doi.org/10.1182/blood-2014-10-551911

Rigel Forward Looking Statements

This press release contains forward-looking statements relating to, among other things, that olutasidenib may provide a meaningful benefit to people with relapsed or refractory acute myeloid leukemia, our ability to commercialize olutasidenib in the U.S. and identify potential partners outside of the U.S., and our expectations related to the potential and market opportunity of olutasidenib as therapeutics for R/R AML and other conditions. Any statements contained in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Forward-looking statements can be identified by words such as "plan", "potential", "may", "expects", "will" and similar expressions in reference to future periods. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on Rigel's current beliefs, expectations, and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions, and hence they inherently involve significant risks, uncertainties and changes in circumstances that are difficult to predict and many of which are outside of our control. Therefore, you should not rely on any of these forward-looking statements. Actual results and the timing of events could differ materially from those anticipated in such forward looking statements as a result of these risks and uncertainties, which include, without limitation, risks that the FDA, EMA or other regulatory authorities may make adverse decisions regarding olutasidenib; risks that clinical trials may not be predictive of real-world results or of results in subsequent clinical trials; risks that olutasidenib may have unintended side effects, adverse reactions or incidents of misuses; the availability of resources to develop Rigel's product candidates; market competition; as well as other risks detailed from time to time in Rigel's reports filed with the Securities and Exchange Commission, including its Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 and subsequent filings. Any forward-looking statement made by us in this press release is based only on information currently available to us and speaks only as of the date on which it is made. Rigel does not undertake any obligation to update forward-looking statements, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise, and expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein, except as required by law.

Investors:
Rigel Pharmaceuticals, Inc.
650.624.1232
ir@rigel.com

Media:
David Rosen
Argot Partners
212.600.1902

david.rosen@argotpartners.com

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