January 4, 2024

Rigel Announces Collaboration with CONNECT to Conduct a Phase 2 Trial of Olutasidenib in Glioma

SOUTH SAN FRANCISCO, Calif., Jan. 4, 2024 /PRNewswire/ -- Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL) today announced a collaboration with CONNECT, an international collaborative network of pediatric cancer centers, to conduct a Phase 2 clinical trial to evaluate REZLIDHIA® (olutasidenib) in combination with temozolomide as maintenance therapy in newly diagnosed pediatric and young adult patients with high-grade glioma (HGG) harboring an isocitrate dehydrogenase-1 (IDH1) mutation.

Under the collaboration, CONNECT will include olutasidenib in CONNECT's TarGeT-D, a molecularly guided Phase 2 umbrella clinical trial for HGG. The Rigel-sponsored arm will study post-radiotherapy administration of olutasidenib in combination with temozolomide followed by olutasidenib monotherapy as maintenance treatment in newly diagnosed pediatric and young adult patients (less than 39 years old) with IDH1 mutation positive HGG, including diffuse intrinsic pontine glioma (DIPG), an aggressive brain tumor with limited treatment options. Rigel will provide funding up to $3 million and study material over the four-year collaboration.

"We are excited to collaborate with CONNECT to evaluate olutasidenib in high grade glioma," said Raul Rodriguez, Rigel's president and CEO. "We believe olutasidenib has potential in a variety of cancers where *m*IDH1 plays an important role and we look forward to generating new data in this disease state, which has a high unmet need. This collaboration builds on our hematology-oncology pipeline expansion strategy and enables us to explore the potential of olutasidenib in a focused and efficient manner."

This open label Phase 2 trial will be overseen by Drs. Santosh Valvi and Nicholas Gottardo, Perth Children's Hospital, Dr. Michael J Fisher, Children's Hospital of Philadelphia, and Dr. Maryam Fouladi, Nationwide Children's Hospital, and aims to enroll approximately 60 patients. The primary objective of the olutasidenib arm of the trial is to estimate progression-free survival. The study will also characterize the safety, tolerability, and pharmacokinetics of olutasidenib in pediatric and young adult patients. The study is estimated to begin enrolling patients in the first half of 2024 and will fulfill Rigel's post-marketing pediatric study requirement related to the FDA approval of REZLIDHIA in relapsed or refractory (R/R) AML.

In January 2023, data was published in the peer-reviewed journal Neuro-Oncology from a

multicenter, open label, Phase 1b/2 trial of 26 patients with R/R and predominantly enhancing gliomas harboring an IDH1 mutation. The data showed that olutasidenib 150 mg BID was well tolerated and demonstrated preliminary evidence of clinical activity and prolonged disease control in this heavily pretreated population. The authors noted that olutasidenib is a potent, brain-penetrant, selective inhibitor of mutant IDH1.[1] The paper, titled "Olutasidenib (FT-2102) in patients with relapsed or refractory IDH1-mutant glioma: A multicenter, open-label, phase Ib/II trial" can be accessed here.

REZLIDHIA is FDA-approved for the treatment of adult patients with R/R acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.

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 of REZLIDHIA 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, visit www.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 therapies that significantly improve the lives of patients with hematologic disorders and cancer. 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.

About CONNECT

CONNECT is an international collaborative network of pediatric cancer centers with the objective to improve outcomes for children with brain tumors. CONNECT conducts small, scientifically rational, pilot and early phase studies to assess feasibility and early efficacy of incorporating promising new therapies into established frontline therapeutic regimens. For more information on CONNECT, visit connectconsortium.org.

1. de la Fuente M, et al. Olutasidenib (FT-2102) in patients with relapsed or refractory IDH1-mutant glioma: A multicenter, open-label, phase Ib/II trial. *Neuro Oncol.* 2023 Jan 5;25(1):146-156. doi: 10.1093/neuonc/noac139.

Forward Looking Statements

This press release contains forward-looking statements relating to, among other things, that olutasidenib may provide a meaningful approach to the treatment of patients with glioma, the enrollment of patients in the Phase 2 study of olutasidenib, and the use of the safety and efficacy data from the Phase 2 study of olutasidenib in glioma. 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 "aims", "expected", "explore" "potential", "look forward", "believe", "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 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 and uncertainties associated with the FDA, European Medicines Agency, PMDA 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 September 30, 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

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View original content to download multimedia:https://www.prnewswire.com/news-releases/rigel-announces-collaboration-with-connect-to-conduct-a-phase-2-trial-of-olutasidenib-in-glioma-302026029.html

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