

December 9, 2024



Rigel Highlights Initial Data from Ongoing Phase 1b Study Evaluating R289 in LR-MDS at the 66th ASH Annual Meeting and Exposition

- *R289 was generally well tolerated and demonstrated signs of preliminary clinical activity in elderly heavily pretreated LR-MDS patients*
- *RBC-TI/HI-E responses occurred in 40% of evaluable TD patients receiving R289 doses ≥ 500 mg QD*

SOUTH SAN FRANCISCO, Calif., Dec. 9, 2024 /PRNewswire/ -- Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL), a commercial stage biotechnology company focused on hematologic disorders and cancer, today announced initial data from its ongoing Phase 1b study evaluating R289¹, an oral prodrug of R835, a potent and selective dual inhibitor of IRAK1 and IRAK4, in patients with relapsed or refractory (R/R) lower-risk myelodysplastic syndrome (LR-MDS). The data is being presented today by Dr. Guillermo Garcia-Manero (Poster #: 4595) at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition being held December 7-10, in San Diego, California and virtually.

"Elderly patients with transfusion dependent LR-MDS have few effective treatment options. We are encouraged by the safety and tolerability profile demonstrated by R289 thus far, and by the first evidence of hematologic responses, namely transfusion independence, observed," said Lisa Rojkjaer, M.D, Rigel's chief medical officer. "The promising initial safety and efficacy data, together with the recent Fast Track designation from the FDA, underscores the potential of R289 as a new treatment option for these patients."

Rigel's open-label, Phase 1b study of R289 is enrolling patients with lower-risk MDS who are R/R to prior therapies ([NCT05308264](https://clinicaltrials.gov/ct2/show/study/NCT05308264)). The primary objective of the study is to assess the safety and tolerability of R289 with secondary objectives to assess preliminary efficacy of R289 and characterize its pharmacokinetic profile.

Key highlights from the interim data as of October 25, 2024, include:

- 22 patients were enrolled. The median age was 76; the median number of prior therapies was 3 (range: 1-8); 73% and 77% of patients had received a hypomethylating agent or luspatерcept, respectively; and 73% of patients were high transfusion burden

(HTB) at baseline.

- The median time on therapy was 4.6 months (range: 0.9-22.4 months). R289 was generally well-tolerated in this heavily pretreated LR-MDS patient population, the majority of whom were HTB. The most common treatment emergent adverse events (in $\geq 20\%$ of patients) were diarrhea and fatigue (each $n=6$, 27%), and chills, nausea and pruritus (all $n=5$, 23%), which were all Grade 1/2. The most frequent Grade 3/4 adverse events (AEs) were anemia, platelet count decreased, pneumonia and alanine aminotransferase (ALT) increased (all $n=2$, 9%). One patient discontinued study drug due to hyperuricemia (not drug related) and a second patient discontinued study due to Grade 3 aspartate aminotransferase (AST)/Grade 4 ALT increase (drug related).
- R835 exposure increased with increasing R289 dose. At doses ≥ 500 mg QD (once daily), R835 plasma concentrations at steady state in some patients were $\geq$ those correlating with 50% or 90% lipopolysaccharide-induced cytokine inhibition previously observed in a healthy volunteer study.
- For the 18 efficacy evaluable patients (≥ 1 dose of R289 with ≥ 1 efficacy assessment), hematologic responses occurred in 40% (4/10) of evaluable transfusion dependent patients receiving R289 doses ≥ 500 mg QD. Red blood cell (RBC)-transfusion independence (RBC-TI) ≥ 8 weeks was achieved by three patients (1 at 500 mg QD and 2 at 750 mg QD); two HTB patients achieved RBC-TI ≥ 24 weeks. The median duration of RBC-TI was 29 weeks (range 12.7-51.9 weeks).
- One HTB patient receiving 500 mg QD achieved a minor hematologic improvement-erythroid (HI-E) response, with a 64% reduction in RBC transfusions compared to baseline.

Additional supporting data:

- The patients achieving RBC-TI had peak hemoglobin increases exceeding 2.0 g/dL compared to baseline.
- There were no RBC-TI/HI-E responses in evaluable transfusion dependence patients receiving R289 doses of 250 mg QD and 250 mg BID.

R289 was recently [granted](#) Fast Track designation by the U.S. Food and Drug Administration for the treatment of patients with previously-treated transfusion dependent LR-MDS.

Poster #: 4595

Title: R289, a Dual IRAK 1/4 Inhibitor, in Patients with Relapsed/Refractory (R/R) Lower-Risk Myelodysplastic Syndrome (LR-MDS): Initial Results from a Phase 1b Study

Session: 637. Myelodysplastic Syndromes: Clinical and Epidemiological: Poster III

Time: Monday, December 9, 2024, 6:00pm to 8:00pm PT

Location: Halls G-H (San Diego Convention Center)

About R289

R289 is a prodrug of R835, an IRAK1/4 dual inhibitor, which has been shown in preclinical studies to block inflammatory cytokine production in response to toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) family signaling. TLRs and IL-1Rs play a critical role in the innate immune response and dysregulation of these pathways can lead to various inflammatory conditions. Chronic stimulation of both these receptor systems is thought to cause the pro-inflammatory environment in the bone marrow responsible for persistent cytopenias in lower-risk MDS patients.²

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.

1. R289 is an investigational compound not approved by the FDA.
2. Sallman DA et al. *Unraveling the Pathogenesis of MDS: The NLRP3 Inflammasome and Pyroptosis Drive the MDS Phenotype*. Front Oncol. June 16, 2016. Accessed September 30, 2024. DOI: <https://doi.org/10.3389/fonc.2016.00151>

Forward-Looking Statements

This press release contains forward-looking statements relating to, among other things, clinical information regarding the progress of Rigel's Phase 1b clinical trial of R289 for the treatment of lower-risk myeloid dysplastic syndrome. 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", "look to", "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 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 clinical trials, and risks that clinical trials may not be predictive of real-world results or of results in subsequent clinical trials; the availability of resources to conduct subsequent clinical trials or 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, 2024 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.

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