Q4 & FY 2023 Financial Results Presentation

March 5, 2024

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1955 ("PSLRA") relating to, among other things, expected commercial and financial results; Rigel's ability to earn and receive milestone payments; expectations related to the potential and market opportunity of REZLIDHIA® (olutasidenib) as therapeutics for relapsed or refractory acute myeloid leukemia (AML) and other conditions; the potential and market opportunity for TAVALISSE® (fostamatinib) as therapeutics for chronic ITP and other conditions; the regulatory approval and commercialization of fostamatinib or olutasidenib in the U.S. and international markets; and Rigel's ability to further develop its clinical stage and early-stage product candidates and Rigel's partnering and collaboration/alliance efforts, including the progress of the Phase 1b clinical trial of R289 for the treatment of lower-risk myeloid dysplastic syndrome (MDS), the advancement of the Phase 2a clinical trial of R552 for the treatment of rheumatoid arthritis, and the development of olutasidenib as a therapy for a broad range of mIDH1+ cancers, including but not limited to AML, MDS, and glioma, and Rigel's partnering efforts and ability to achieve regulatory and commercial milestones and earn and receive milestone payments; and the potential benefits of Rigel's acquisition of U.S. rights to GAVRETO (pralsetinib), including opportunities in NSCLC and DTC, Rigel's ability to leverage its existing commercial infrastructure to market and distribute pralsetinib, Rigel's ability to transition pralsetinib to its distribution network and provide patients with access to pralsetinib, the payment and timing of milestone and royalty payments and Rigel's ability to start recognizing product sales in the third quarter of 2024 and the market opportunity for pralsetinib.

Any statements contained in this presentation that are not statements of historical fact may be deemed to be forward-looking statements and as such are intended to be covered by the safe harbor for "forward-looking statements" provided by the PSLRA. 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 and hence they inherently involve significant risks, uncertainties and changes in circumstances that are difficult to predict and many of which are outside of Rigel's 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 commercialization and marketing of fostamatinib, olutasidenib or pralsetinib; risks that the FDA, European Medicines Agency, PMDA or other regulatory authorities may make adverse decisions regarding fostamatinib, olutasidenib or pralsetinib; risks that clinical trials may not be predictive of real-world results or of results in subsequent clinical trials; risks that fostamatinib, olutasidenib or pralsetinib may have unintended side effects, adverse reactions or incidents of misuses; the availability of resources to develop, manufacture and commercialize Rigel's product candidates; market competition; and those other risks detailed from time to time in Rigel's reports filed with the Securities and Exchange Commission, including its Annual Report on Form 10-K for the year ended December 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.

Rigel Participants

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Growing Our Hematology and Oncology Business

Commercial Execution

Tavalisse® (fostamatinib disodium hexahydrate) tablets

ITP

REZLIDHIA® (olutasidenib) 150 mg capsules

mIDH1 R/R AML

Expansion & Development

In-Licensing and Product Acquisition

- GAVRETO®(pralsetinib) added to existing commercial and medical affairs operations
- New late-stage assets which leverage current capabilities and capacity

Development Programs[1]

- Evaluate REZLIDHIA in a broad range of IDH1-mutant cancers including AML, MDS and glioma
- R289 IRAK1/4 inhibitor Phase 1b trial in lower-risk MDS

1. Investigational compounds in these indications and not approved by the FDA. Please see Important Safety Information on slides 32-36. Please visit www.TAVALISSE.com for Full Prescribing Information. Please visit www.REZLIDHIA.com for Full Prescribing Information, including Boxed WARNING. Please visit www.GAVRETO.com for Full Prescribing information.

Acquired U.S. Rights to GAVRETO®

GAVRETO (pralsetinib) is a once daily, small molecule, oral, kinase inhibitor of wild-type RET (rearranged during transfection) and oncogenic RET fusions

Highly synergistic with Rigel's current product portfolio and existing commercial infrastructure and expertise

Generated **~$28M** in U.S. net product sales in 2023[1]

Patents that have issued or are expected to issue covering GAVRETO will have statutory expiration dates between 2036 and 2041

- **Established U.S. marketed product**
- Blueprint will receive a purchase price of **$15.0M**
  - **$10.0M** payable upon first commercial sale by Rigel
  - **$5.0M** payable on the first anniversary of the closing date, subject to certain conditions
- Blueprint is also eligible to receive up to $97.5M in future commercial milestone payments and up to $5.0M in future regulatory milestone payments, in addition to tiered royalties ranging from 10% to 30%
- Rigel expects to add GAVRETO to its operations and start recognizing product sales in Q3, 2024

1. US Net sales provided by Blueprint Medicines as reported by Genentech, a member of the Roche group. Please see Important Safety Information on slides 35 & 36. Please visit www.GAVRETO.com for Full Prescribing information.

APPROVED IN THE U.S.

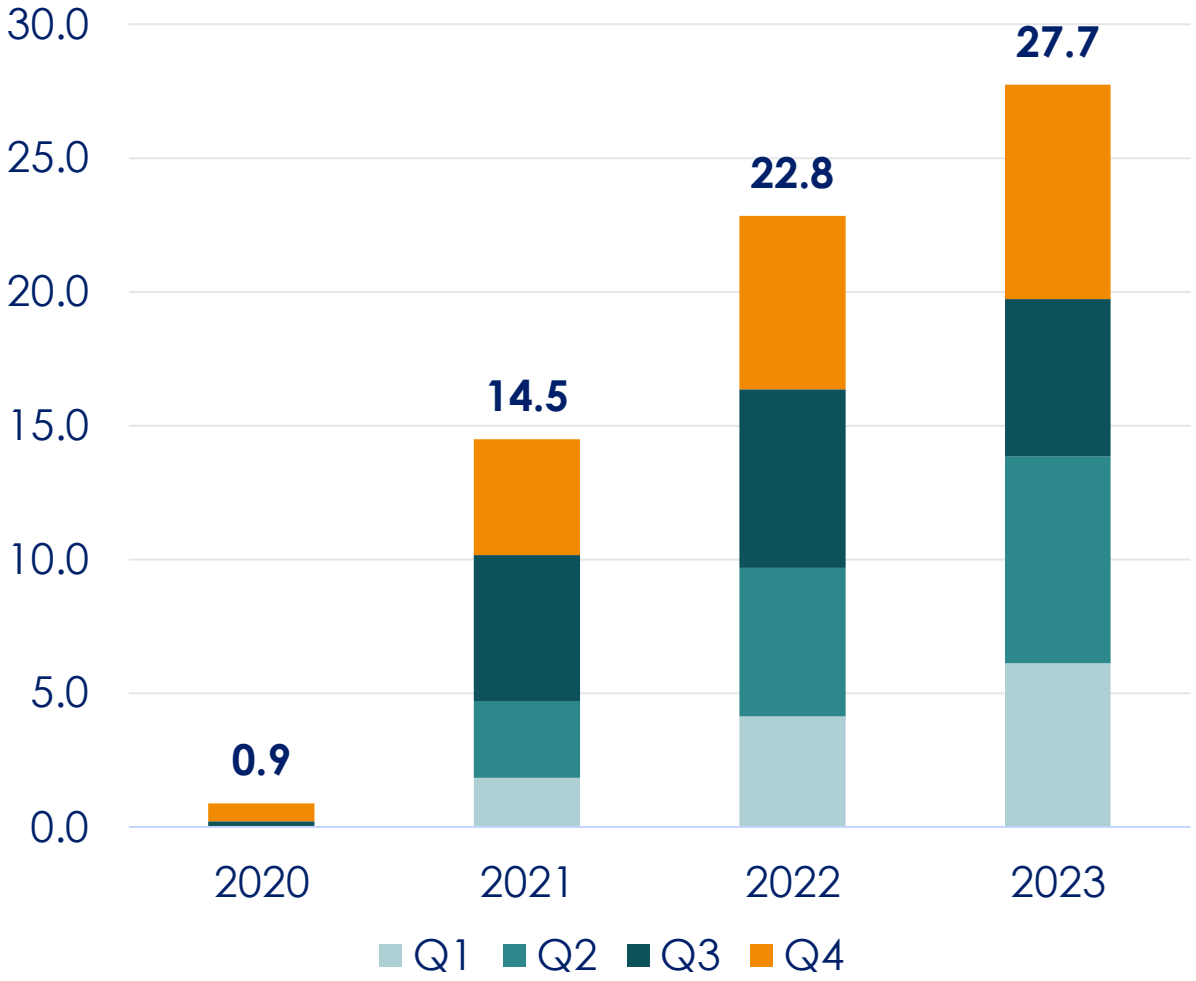
GAVRETO is indicated for the treatment of adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer as detected by an FDA-approved test, and adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)*

Please see Important Safety Information on Slides 35 and 36

* This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Growing Our Oncology Targeted Therapy Portfolio

GAVRETO US Net Sales ($M)[1]



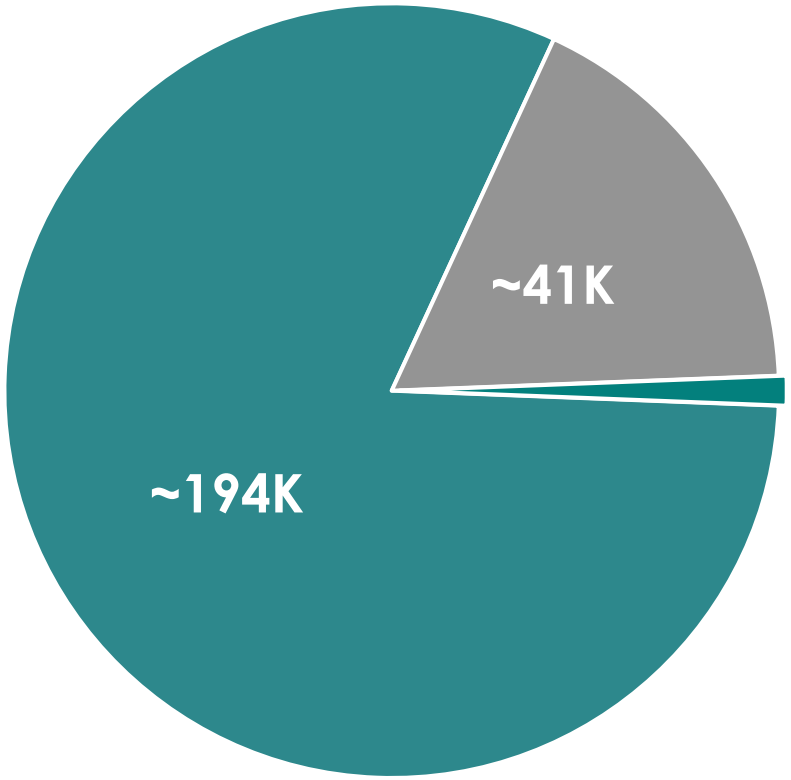
A compelling and synergistic opportunity

- Enables entry into a well-identified subset of large solid tumor market
  - Immediately recognizable population of RET fusion-positive patients
  - Challenging to treat with platinum-based chemotherapy and checkpoint inhibitors
- Leverages patient access
  - Efficient product distribution
  - Responsive Rigel ONECARE patient services
  - Strong coverage and reimbursement
- Complementary to our field capabilities
  - Commercial and Medical Affairs teams in both academic and community settings

1. US Net sales provided by Blueprint Medicines as reported by Genentech, a member of the Roche group.

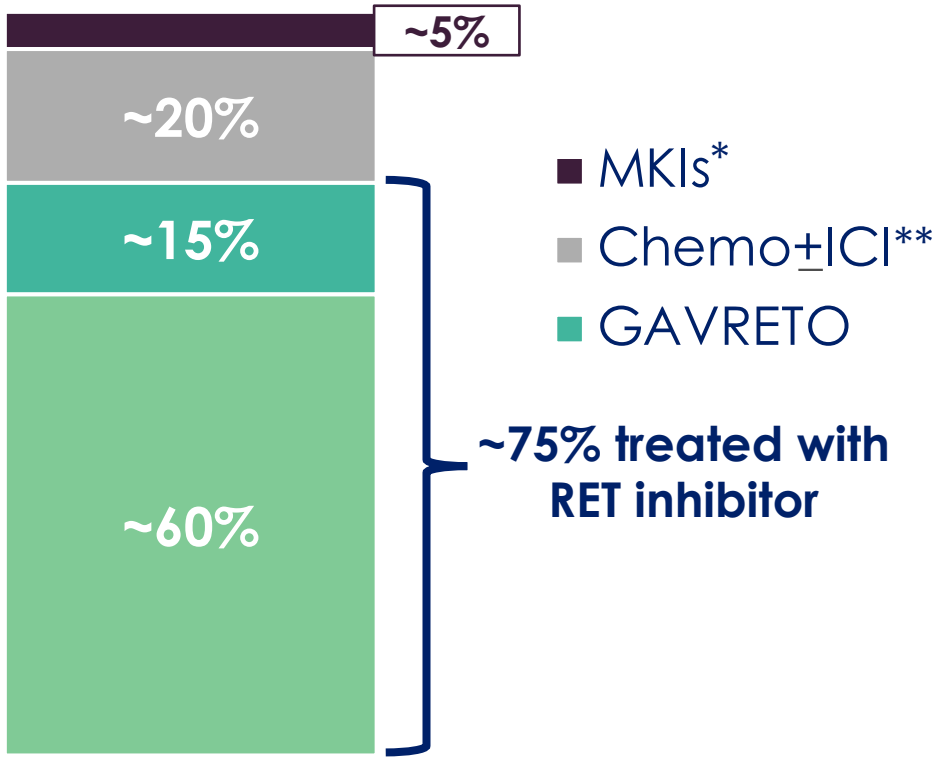
NSCLC and Treatment of RET fusion-positive Patients

~235K Lung cancer patients in 2024[1]



~3K RET fusion-positive patients[2]

1L therapy for treatment eligible patients[3]



* Multi-Kinase Inhibitors
** Immune Checkpoint Inhibitors(anti PD-1/PD-L1)

NSCLC = Non-Small Cell Lung Cancer. 1. American Cancer Society Key Statistics for Lung Cancer https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html 2. Kato, S. et al. RET aberrations in diverse cancers: next-generation sequencing of 4,871 patients. Clin Cancer Res. 2017;23(8):1988-1997 doi: 10.1158/1078-0432.CCR-16-1679 3. Market Research conducted in Q2 2023 with 60 oncologists managing RET fusion-positive patients

Pralsetinib Clinical Data Overview

RET-altered Solid Tumors Have Been Underserved Historically[1,2,3,4,5]

Disease Overview

- RET is one of the first oncogenic kinase fusions cloned from an epithelial tumor, an oncogenic driver primarily in solid tumors
- **Two primary mechanisms**: fusions and activating mutations
- **RET alterations are prevalent across a range of tumors:**

	 NSCLC[1,2]	 Papillary thyroid cancers[3]
RET fusions	~1-2%	~20%
US annual patient incidence	~3K	~1K

Historical Medical Need

- **Non-selective therapies in RET+ NSCLC have poor outcomes with an ORR <30%**
- **Sub-optimal inhibition impacts the durability of responses with non-selective multi-kinase inhibitors**
- **Drug-related toxicity due to non-selective inhibitors has been evidenced by poor tolerability**
- **Up to 75% of patients dose reduce due to poor tolerability of non-selective inhibitors**

1. Lipson, et al. Nat Med 2012 2. Takeuchi, et al. Nat Med 2012 3. Santoro, et al. J Clin Invest 1992 4. Romei, et al. Oncotarget 2018 5. Gainor JF. et al., BLU-667 ASCO 2019 Presentation

MKIs, Platinum-based Therapies and Immunotherapies are Associated with Suboptimal Response Rates and PFS

Studies Evaluating Kinase Inhibitors in Patients with RET Fusion-positive NSCLC

	Outcomes	ORR (%)	Median PFS (months)
MKI	Vandetanib, Cabozantinib, Lenvatinib, Sorafenib[1,2,3,4,5]	0 - 28%	4.5-7.3
	Anti-PD1/PD-L1 directed immune checkpoint inhibitors (ICI) [6]	6%	2.1
	Pemetrexed/platinum-based therapy (n=66)[7]	49%	6.4
	Platinum based chemotherapy (n=84)[7]	51%	7.8

NOTE: Data is from independent studies, not comparative trials.

Multi-kinase inhibitors: Discontinuation rate 8-24% and rate of AEs grade ≥ 3, 28-92%

1. Drilon A et al. *Nat Rev Clin Oncol* 15, 151–167 (2018). 2. Lee SH et al. *Annals of Oncology*. 2017;28(2):292-297. 3. Drilon A et al. *Lancet Oncology*. 2016;17(12):1653- 1660. 4. Hida T et al. *Lung Cancer*. 2019;138:124-136. 5. Horiike A et al. *Lung Cancer*. 2016;93:43-46. doi:10.1016/j.lungcan.2015.12.011. 6. Mazieres J, Drilon AE, Mhanna L, et al. Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget). *Journal of clinical oncology* 7. Gautschi O, et al. Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry. J Clin Oncol. 2017;35(13):1403. Epub 2017 Mar 13.

Targeted Therapies May Lead to Better Outcomes in Patients with Biomarker Driven Cancers

- Evolution towards a biomarker driven strategy in NSCLC
- Pralsetinib is an oral tyrosine kinase inhibitor that selectively and potently targets oncogenic RET fusions and mutations and has very low affinity for other kinases[1,2]
  - 81-fold more selective for RET than VEGFR2 in a biochemical assay
  - 20-fold more selective for RET than JAK1 in a biochemical assay
- Pralsetinib has shown antitumor activity in various preclinical RET-altered tumor models, including intracranially implanted tumors[1,2]
- Practice guidelines recommend targeted therapies as first-line treatment for eligible patients with metastatic NSCLC who have actionable genetic variants

JAK1, Janus kinase VEGFR2, vascular endothelial growth factor receptor

1. Subbiah V et al. Presented at ASCO Annual Meeting 2021. Abstract 109 2. Gainor J et al. Presented at ASCO Annual Meeting 2019. Abstract 9008

Pralsetinib Has Shown Profound Clinical Benefit with Transformative Response Rates Regardless of Treatment History[1]

Phase 1: Dose Escalation

Pralsetinib: 30–600mg QD or BID

Phase 2: Expansion Cohorts

RET-altered advanced solid tumors

RP2D: ***400mg QD***

ARROW: Phase 1/2 Dose-escalation and Expansion Study

RET fusion+ NSCLC

RET fusion+TC (N=22)

Other RET fusion+ solid tumors (N=23)

Previously treated NSCLC (n=130)[1]

ORR: 63%

ORR: 91%

Treatment-naïve NSCLC (n=107)[1]

ORR: 74–80%

ORR: 57%

In the NSCLC subset, median duration of response was 19.1 months (14.5-27.3)[1]

Note: QD = Once Daily; BID = Twice Daily Dosing

1. ESMO 2022 measurable disease population results, Besse B et al. Presented at ESMO Annual Meeting 2022. Poster 1170P

The Development of CNS Metastases is Common and a Poor Prognostic Factor in Patients with RET fusion-positive NSCLC[1]

Data cutoff: March 4, 2022

Pralsetinib CNS Efficacy in RET fusion–positive NSCLC[2]

	All (n=15)
CNS ORR, % (95% CI)	53.3 (26.6–78.7)
CR, n (%)	3 (20.0)
PR, n (%)	5 (33.3)
	n=8
Median DOR, months (95% CI)[a]	11.5 (9.2–NR)
Median follow-up (95% CI)	29.7 (24.1–35.3)

25% of Stage 4 RET fusion-positive lung cancer have brain metastases at baseline[1]

[a]Per EMA censoring rule.
CI, confidence interval; CNS, central nervous system; CR, complete response; DOR, duration of response; EMA, European Medicines Agency; NSCLC, non-small cell lung cancer; PR, partial response.

1. Drilon A, Lin JJ, Filleron T, et al. Frequency of brain metastases and multikinase inhibitor outcomes in patients with RET-rearranged lung cancers. J Thorac Oncol 2018; 13: 1595–601. 2. Besse B et al. Presented at ESMO Annual Meeting 2022. Poster 1170P

Pralsetinib Has a Differentiated Value Proposition

The **only once daily, oral,** precision therapy that selectively and potently inhibits RET alterations

High and durable response rates regardless of treatment history

Clinically proven to cross the **blood-brain barrier**

Established **safety and tolerability** profile

Practice guidelines **recommended treatment option for patients with RET+ mNSCLC and advanced thyroid cancer**

GAVRETO Commercialization Plans

Leveraging Rigel's Capabilities to Ensure Patient Access

Distribution

- Rigel's wholesaler network matches >95% to current Genentech network
- Rigel will maintain a limited specialty pharmacy network, consistent with our other portfolio.

Patient Services

rigel onecare®

- Over 7 years of experience in rare diseases working with patients, providers, & payers
- Experience in moving patients into a limited SP network
- Rigel programs largely match what patients have experienced at previous manufacturers.

Reimbursement and Coverage

Tavalisse®
(fostamatinib disodium hexahydrate) tablets

97% Commercial Coverage

- Strong existing relationships with PBMs and GPOs will help maintain patient access to GAVRETO

rigel

Committed to Access Without Interruption

Ready to serve current and newly prescribed patients

- Rigel's Limited Network will ensure provider and patient choice
- Staff dedicated to GAVRETO at RIGEL ONECARE will ensure high customer service
- New patients enter the network via RIGEL ONECARE or directly to Rigel's established network
- Transfer of patients will be completed in Q3 2024

Key Drivers for Continued GAVRETO Growth

Patient Identification[1]

- Awareness of the RET biomarker being associated with an FDA approved therapy is high and stable at ~90%
- RET testing rate has directionally increased to ~80% of 1L NSCLC patients being tested
  - Testing rates are similar between academic and community oncologists
  - Inadequate tissue for testing is the top barrier to NSCLC RET testing, even in squamous patients

Choice of therapy in treatment eligible patients[1]

- 80% of oncologists in 2023 survey were GAVRETO non-users in 1L RET fusion-positive patients
  - Top barrier for use was comfort and familiarity with other drugs

Significant carryover through persistency

- High response rates with long duration combined with convenient once-daily dosing

Coverage, reimbursement, and patient services

- Out-of-pocket cost and difficulty obtaining reimbursement are top barriers for RET inhibitor adoption[1]

1. Market Research conducted in Q2 2023 with 60 oncologists managing RET fusion-positive patients

2024 Commercialization Timeline

GAVRETO® pralsetinib | 100mg capsules

Q1
- Prepare distribution network

Q2
- RIGEL ONECARE implements plan to transition current and newly prescribed GAVRETO patients
- Prepare field teams

Q3
- Begin distributing and promoting GAVRETO to customers
- Focus on GAVRETO users

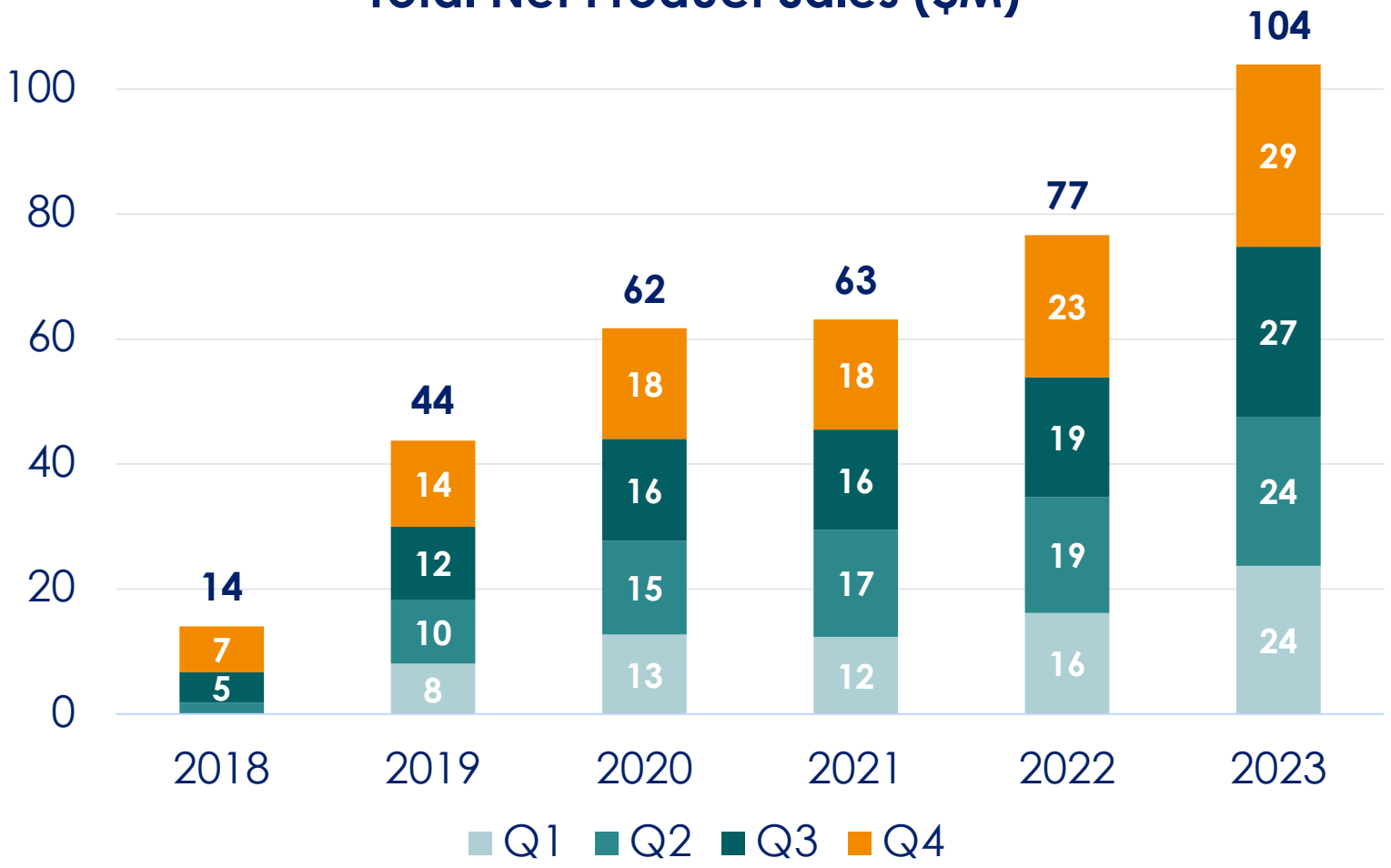
Q4
- Continue expanding breadth of prescribers
- Increase Academic and Community awareness

rigel®

TAVALISSE and REZLIDHIA 2023 Results

Growing Annual Sales of TAVALISSE and REZLIDHIA

Total Net Product Sales ($M)



2023 Highlights

- Generated $104.3M in full-year net product sales
  - 36% ($28M) growth vs. 2022
- TAVALISSE generated $93.7M
  - 24% ($18M) growth vs. 2022
- REZLIDHIA generated $10.6M
  - 45% growth in Q4 vs. Q3

Development Programs Update

Hematology and Oncology Pipeline Expansion

Development Opportunities[1]

Olutasidenib

- Evaluate olutasidenib in a broad range of IDH1-mutant cancers including AML, MDS and glioma

R289 IRAK1/4 Inhibitor

- Evaluate in lower-risk MDS

Fostamatinib

- Evaluate heme/onc opportunities through investigator sponsored trials

Leverage Heme/Onc Capabilities

In-Licensing & Product Acquisition

- Differentiated asset(s) in hematology, oncology or related areas
- Late-stage programs
- Synergistic to current in-house capabilities and capacity

1. Investigational compounds in these indications and not approved by the FDA

Strategic Alliance with MD Anderson to Advance REZLIDHIA (olutasidenib) in AML and Other Cancers[1]

- Rigel and The University of Texas MD Anderson Cancer Center will evaluate olutasidenib, in combination with other agents, to treat newly diagnosed and relapsed or refractory patients with:
  - AML
  - Higher-risk MDS and advanced MPN
- The collaboration will also support the evaluation of olutasidenib as:
  - Monotherapy in CCUS & lower-risk MDS
  - Maintenance therapy in post-HSCT patients

Rigel will provide $15 million in time-based milestone payments and study material over the 5-year collaboration

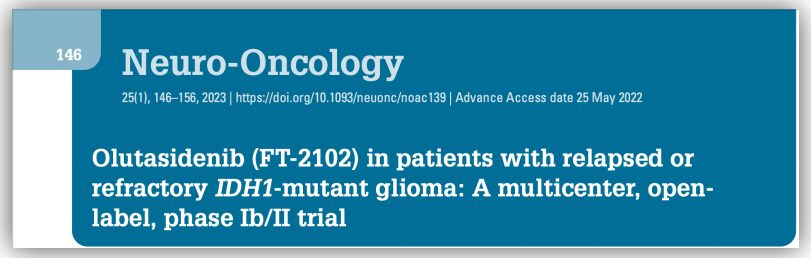
CCUS = Clonal Cytopenia of Undetermined Significance 1. Investigational compound in these indications and not approved by the FDA. Please see Important Safety Information on slides 35 & 36. Please visit www.REZLIDHIA.com for Full Prescribing Information, including Boxed WARNING.

Potential Olutasidenib Opportunity in Glioma[1]

High Unmet Need Remains in Glioma

- Gliomas are a heterogeneous group of primary brain tumors that are associated with diffuse brain infiltration and premature death.[2,3]
- Diffuse gliomas are the most common primary brain tumor in adults, affecting about 20,000 people in the US each year.[4]
- More than 70% of patients with grades II/III and approximately 5–7% of patients with grade IV harbor IDH1 mutations.[5, 6]
- Standard of care for gliomas is best supportive care based on surgery, radiation, and chemo-therapies that are not very effective.
- There is a significant unmet need to improve survival.

Olutasidenib Activity in Enhancing Gliomas[7]



- 26 patients with R/R glioma received olutasidenib 150 mg orally BID
- No DLTs were observed in the single-agent glioma cohort
- Disease control rate (OR+ SD) was 48%.
  - 2 PR and 8 SD for at least 4 months.
  - Grade 3–4 adverse events (≥10%) included alanine aminotransferase increased (12%) and aspartate aminotransferase increased (12%)
- Olutasidenib was well tolerated, demonstrated preliminary evidence of clinical activity, and prolonged disease control in patients with predominantly enhancing gliomas with IDH1 mutation

1. Investigational compound in this indication and not approved by the FDA. 2. van den Bent et al., Diffuse infiltrating oligodendroglioma and astrocytoma. J. Clin. Oncol. 2017;35:2394–2401. doi: 10.1200/JCO.2017.72.6737. 3. Wen et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. NeuroOncology. 2020;22:1073–1113. doi: 10.1093/neuonc/noaa106. 4. Lapointe et al.,Primary brain tumours in adults. Lancet. 2018 Aug 4;392(10145):432-446. doi: 10.1016/S0140-6736(18)30990-5. 5. Yan et al., IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009 Feb 19;360(8):765-73. doi: 10.1056/NEJMoa0808710. 6. Myung et al., IDH1 mutation of gliomas with long-term survival analysis. Oncol Rep. 2012 Nov;28(5):1639-44. doi: 10.3892/or.2012.1994. 7. de la Fuente 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.

Collaboration with CONNECT to Conduct a Phase 2 Trial of Olutasidenib in Glioma[1]

- Olutasidenib will be included in CONNECT's TarGeT-D, a molecularly guided Phase 2 umbrella clinical trial for HGG
- Rigel and CONNECT will evaluate olutasidenib in newly diagnosed pediatric and young adult patients (<39 years) with high-grade glioma (HGG) harboring an IDH1 mutation
- The Rigel-sponsored arm will study post-radiotherapy administration of olutasidenib in combination with temozolomide followed by olutasidenib monotherapy as maintenance treatment

Rigel will provide funding up to $3 million and study material over the 4-year collaboration

1. Investigational compound in this indication and not approved by the FDA.

Financials

Q4 2023 Financial Highlights

Q4 '23 Net Product Sales:

- TAVALISSE: $25.7M
- REZLIDHIA: $3.9M

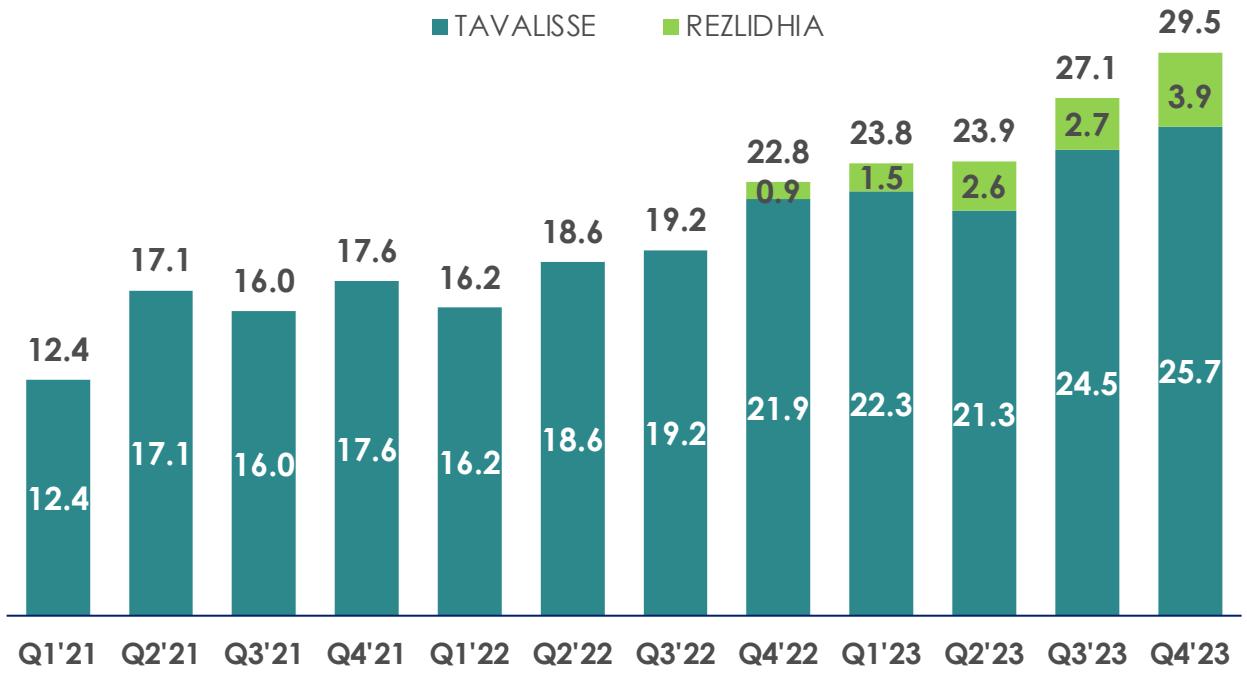
Q4 '23 Total Bottles Shipped:

- TAVALISSE: 2,671
- REZLIDHIA: 308

Q4 '23 Bottles Shipped to Patients and Clinics[1]:

- TAVALISSE: 2,463
- REZLIDHIA: 278

Net Product Sales ($M)



1. 1,374 total TAVALISSE bottles, net of returns, and 98 total REZLIDHIA bottles, net of returns, remained in distribution channels as of December 31, 2023.

Q4 2023 Financial Results

(In thousands, except for per share amounts)

	Three Months Ended December 31,		Year Ended December 31,	
	2023	2022	2023	2022
Revenues				
Net Product Sales	$ 29,539	$ 22,783	$ 104,294	$ 76,718
Contract revenues from collaborations	6,153	26,495	11,488	39,024
Government contract	100	2,000	1,100	4,500
Total revenues	35,792	51,278	116,882	120,242
Costs and expenses:				
Cost of product sales	3,790	342	7,110	1,749
Research and development	3,186	15,365	24,522	60,272
Selling, general and administrative	26,850	32,172	105,741	112,451
Restructuring charges	-	1,320	-	1,320
Total costs and expenses	33,826	49,199	137,373	175,792
Income (loss) from operations	1,966	2,079	(20,491)	(55,550)
Interest income	678	429	2,272	684
Interest expense	(1,907)	(1,107)	(6,872)	(3,707)
Net income (loss)	$ 737	$ 1,401	$ (25,091)	$ (58,573)
Net income (loss) per share, basic	$ 0.00	$ 0.01	$ (0.14)	$ (0.34)
Net income (loss) per share, diluted	$ 0.00	$ 0.01	$ (0.14)	$ (0.34)
Weighted average shares used in computing net income (loss per share, basic	174,376	172,851	173,897	172,406
Weighted average shares used in computing net income (loss_ per share, diluted	174,468	172,856	173,897	172,406

- In Q4 2023, contract revenues from collaborations of **$6.2M** included:
  - Grifols $3.7M
  - Kissei $2.2M
  - Medison $0.3M
- Government contract revenue of **$0.1M**
- Cash, cash equivalents & short-term investment balance totaled **$56.9M** as of December 31, 2023

2024 Value Drivers

Expanding Product Sales for TAVALISSE and REZLIDHIA

- Continue to broaden TAVALISSE and REZLIDHIA awareness and adoption
- Identify ex-US collaboration(s) for olutasidenib

Commercialize GAVRETO

- Effectively add to Rigel's commercial business

Continued Financial Discipline

Development Programs[1]

- Advance olutasidenib in AML, MDS, glioma and other cancers
- Evaluate additional clinical development opportunities and alliances for olutasidenib
- Evaluate heme/onc opportunities for fostamatinib
- Enroll and generate preliminary data for R289 Phase 1b study in lower-risk MDS

In-License and Product Acquisition Opportunities

- Actively pursue new late-stage assets which leverage current capabilities & capacity

1. Investigational compounds in these indications and not approved by the FDA. Please see Important Safety Information on slides 32-36. Please visit www.TAVALISSE.com for Full Prescribing Information. Please visit www.REZLIDHIA.com for Full Prescribing Information, including Boxed WARNING. Please visit www.GAVRETO.com for Full Prescribing information.

TAVALISSE® (fostamatinib disodium hexahydrate) Tablets

INDICATION

- TAVALISSE® (fostamatinib disodium hexahydrate) tablets is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

IMPORTANT SAFETY INFORMATION | WARNINGS AND PRECAUTIONS

- Hypertension can occur with TAVALISSE treatment. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects. Monitor blood pressure every 2 weeks until stable, then monthly, and adjust or initiate antihypertensive therapy for blood pressure control maintenance during therapy. If increased blood pressure persists, TAVALISSE interruption, reduction, or discontinuation may be required.
- Elevated liver function tests (LFTs), mainly ALT and AST, can occur with TAVALISSE. Monitor LFTs monthly during treatment. If ALT or AST increase to ≥3 x upper limit of normal, manage hepatotoxicity using TAVALISSE interruption, reduction, or discontinuation.
- Diarrhea occurred in 31% of patients and severe diarrhea occurred in 1% of patients treated with TAVALISSE. Monitor patients for the development of diarrhea and manage using supportive care measures early after the onset of symptoms. If diarrhea becomes severe (≥Grade 3), interrupt, reduce dose or discontinue TAVALISSE.
- Neutropenia occurred in 6% of patients treated with TAVALISSE; febrile neutropenia occurred in 1% of patients. Monitor the ANC monthly and for infection during treatment. Manage toxicity with TAVALISSE interruption, reduction, or discontinuation.
- TAVALISSE can cause fetal harm when administered to pregnant women. Advise pregnant women the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. Verify pregnancy status prior to initiating TAVALISSE. It is unknown if TAVALISSE or its metabolite is present in human milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during TAVALISSE treatment and for at least 1 month after the last dose.

DRUG INTERACTIONS

- Concomitant use of TAVALISSE with strong CYP3A4 inhibitors increases exposure to the major active metabolite of TAVALISSE (R406), which may increase the risk of adverse reactions. Monitor for toxicities that may require a reduction in TAVALISSE dose.
- It is not recommended to use TAVALISSE with strong CYP3A4 inducers, as concomitant use reduces exposure to R406.
- Concomitant use of TAVALISSE may increase concentrations of some CYP3A4 substrate drugs and may require a dose reduction of the CYP3A4 substrate drug.
- Concomitant use of TAVALISSE may increase concentrations of BCRP substrate drugs (eg, rosuvastatin) and P-Glycoprotein (P-gp) substrate drugs (eg, digoxin), which may require a dose reduction of the BCRP and P-gp substrate drug.

ADVERSE REACTIONS

- Serious adverse drug reactions in the ITP double-blind studies were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis, which occurred in 1% of TAVALISSE patients. In addition, severe adverse reactions occurred including dyspnea and hypertension (both 2%), neutropenia, arthralgia, chest pain, diarrhea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope, and hypoxia (all 1%).
- Common adverse reactions (≥5% and more common than placebo) from FIT-1 and FIT-2 included: diarrhea, hypertension, nausea, dizziness, ALT and AST increased, respiratory infection, rash, abdominal pain, fatigue, chest pain, and neutropenia.

Please see http://www.tavalisse.com/ for full Prescribing Information

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

About REZLIDHIA® (olutasidenib)

INDICATION

REZLIDHIA is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible 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

IMPORTANT SAFETY INFORMATION (Cont.)

WARNINGS AND PRECAUTIONS

Hepatotoxicity

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.

Please see REZLIDHIA.com for Full Prescribing Information, including Boxed WARNING

About GAVRETO® (pralsetinib)

INDICATIONS

GAVRETO (pralsetinib) is indicated for the treatment of:

- Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA-approved test
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)*

*This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

- **Interstitial Lung Disease (ILD)/Pneumonitis:** Severe, life-threatening, and fatal ILD/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 12% of patients who received GAVRETO, including 3.3% with Grade 3-4, and 0.2% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

- **Hypertension:** Occurred in 35% of patients, including Grade 3 hypertension in 18% of patients. Overall, 8% had their dose interrupted and 4.8% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

- **Hepatotoxicity:** Serious hepatic adverse reactions occurred in 1.5% of patients treated with GAVRETO. Increased aspartate aminotransferase (AST) occurred in 49% of patients, including Grade 3 or 4 in 7% and increased alanine aminotransferase (ALT) occurred in 37% of patients, including Grade 3 or 4 in 4.8%. The median time to first onset for increased AST was 15 days (range: 5 days to 2.5 years) and increased ALT was 24 days (range: 7 days to 3.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

- **Hemorrhagic Events:** Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥3 events occurred in 4.1% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

- **Tumor Lysis Syndrome (TLS):** Cases of TLS have been reported in patients with medullary thyroid carcinoma receiving GAVRETO. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

IMPORTANT SAFETY INFORMATION (Cont.)

- **Risk of Impaired Wound Healing:** Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

- **Embryo-Fetal Toxicity:** Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the last dose.

- **Common adverse reactions (≥25%)** were musculoskeletal pain, constipation, hypertension, diarrhea, fatigue, edema, pyrexia, and cough. **Common Grade 3/4 laboratory abnormalities (≥2%)** were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased leukocytes, decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased calcium (corrected), decreased platelets, increased alkaline phosphatase, increased potassium, decreased potassium, and increased bilirubin.

- Avoid coadministration of GAVRETO with **strong or moderate CYP3A inhibitors, P-gp inhibitors, or combined P-gp and strong or moderate CYP3A inhibitors.** If coadministration cannot be avoided, reduce the GAVRETO dose. Avoid coadministration of GAVRETO with **strong or moderate CYP3A inducers**. If coadministration cannot be avoided, increase the GAVRETO dose.

- **Lactation:** Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the last dose.

- **Pediatric Use:** Monitor open growth plates in adolescent patients. Consider interrupting or discontinuing GAVRETO if abnormalities occur.

You may report side effects to the FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**. You may also report side effects to Genentech at **1-888-835-2555.**

Please see https://GAVRETO.com for Full Prescribing Information and Patient Information

Thank You

www.rigel.com