Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 ("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 misuse; 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.
Growing Our Hematology and Oncology Business

Commercial Execution

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

- 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

ITP, immune thrombocytopenia; IDH1, isocitrate dehydrogenase-1; mIDH1, mutated IDH1; R/R, relapsed or refractory; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; IRAK1/4, interleukin receptor-associated kinases 1 and 4.1, Investigational compounds in these indications and not approved by the FDA. Please see Important Safety Information on slides 50-54. 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.


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**
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 53 & 54

* 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

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

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

GAVRETO U.S. Net Sales ($M)$

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>2021</td>
<td></td>
<td>14.5</td>
<td></td>
<td></td>
<td>15.4</td>
</tr>
<tr>
<td>2022</td>
<td></td>
<td></td>
<td>22.8</td>
<td></td>
<td>22.8</td>
</tr>
<tr>
<td>2023</td>
<td></td>
<td></td>
<td></td>
<td>27.7</td>
<td>27.7</td>
</tr>
</tbody>
</table>
NSCLC and Treatment of RET fusion-positive Patients

~235K Lung cancer patients in 2024¹

~3K RET fusion-positive patients²

~194K

~41K

NSCLC (80-85%)  SCLC (15-20%)

1L therapy for treatment eligible patients³

~75% treated with RET inhibitor

MKIs*  Chemo+ICI**  GAVRETO

~60%

~15%

~20%

~5%

¹ 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**

### 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:

<table>
<thead>
<tr>
<th>RET fusions</th>
<th>NSCLC(^1,2)</th>
<th>~1-2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary thyroid cancers(^3)</td>
<td>~20%</td>
<td></td>
</tr>
</tbody>
</table>

| US annual patient incidence | ~3K | ~1K |

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### 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.

---

**NSCLC**, non-small cell lung cancer; RET, rearranged during transfection; ORR, overall response rate.

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ORR (%)</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandetanib, Cabozantinib, Lenvatinib, Sorafenib1,2,3,4,5</td>
<td>0 - 28%</td>
<td>4.5-7.3</td>
</tr>
<tr>
<td>Anti-PD1/PD-L1 directed immune checkpoint inhibitors (ICI) 6</td>
<td>6%</td>
<td>2.1</td>
</tr>
<tr>
<td>Pemetrexed/platinum-based therapy (n=66)7</td>
<td>49%</td>
<td>6.4</td>
</tr>
<tr>
<td>Platinum based chemotherapy (n=84)7</td>
<td>51%</td>
<td>7.8</td>
</tr>
</tbody>
</table>

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

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

MKI, multi-kinase inhibitors; ICI, immune checkpoint inhibitors; PFS, progression-free survival; ORR, overall response rate; NSCLC, non-small cell lung cancer; RET, rearranged during transfection.

• 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

NSCLC, non-small cell lung cancer; RET, rearranged during transfection; JAK1, Janus kinase 1; VEGFR2, vascular endothelial growth factor receptor 2.
Pralsetinib Has Shown Marked Clinical Benefit with High Response Rates Regardless of Treatment History\(^1\)


**Phase 1: Dose Escalation**
- **Pralsetinib:** 30–600mg QD or BID
- **RET-altered advanced solid tumors**
- **RP2D:** 400mg QD

**Phase 2: Expansion Cohorts**
- **RET fusion+ NSCLC**
- **RET fusion+TC** (N=22)
- **Other RET fusion+ solid tumors** (N=23)

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

**Previously treated NSCLC (n=130)\(^1\)**
- **Fusion partner**
  - KIF5B
  - Other
  - CCDC6
- **ORR:** 57%

**Treatment-naïve NSCLC (n=107)\(^1\)**
- **Fusion partner**
  - KIF5B
  - Other
  - CCDC6
- **ORR:** 74–80%

**Phase 1:**
- **Dose Escalation**
  - **Pralsetinib:** 30–600mg QD or BID

**Phase 2:**
- **Expansion Cohorts**
  - **RET fusion+ NSCLC**
  - **RET fusion+TC** (N=22)
  - **Other RET fusion+ solid tumors** (N=23)

**In the NSCLC subset, median duration of response was 19.1 months (14.5-27.3)\(^1\)**

**ORR:** 63%

**ORR:** 91%

**ORR:** 57%

1. QD, once daily; BID, twice daily dosing; RP2D, recommended phase 2 dose; TC, thyroid cancer; ORR, overall response rate; NSCLC, non-small cell lung cancer; RET, rearranged during transfection.
The Development of CNS Metastases is Common and a Poor Prognostic Factor in Patients with RET fusion-positive NSCLC

Post Hoc Analysis of Pralsetinib CNS Efficacy in RET fusion–positive NSCLC

<table>
<thead>
<tr>
<th>All (n=15)*</th>
<th>CNS ORR, % (95% CI)</th>
<th>53.3 (26.6–78.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>5 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>

| Median DOR, months (95% CI)a | Median follow-up (95% CI) | 11.5 (9.2–NR) | 29.7 (24.1–35.3) |

Data cutoff: March 4, 2022

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

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*Per EMA censoring rule.
CI, confidence interval; CNS, central nervous system; CR, complete response; DOR, duration of response; NSCLC, non-small cell lung cancer; PR, partial response, ORR, overall response rate; RET, rearranged during transfection.

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 efficacy in patients with CNS metastasis

- Established safety and tolerability profile

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

RET, rearranged during transfection; CNS, central nervous system; mNSCLC, metastatic non-small cell lung 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**
- 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**
- Strong existing relationships with PBMs and GPOs will help maintain patient access to GAVRETO (pralsetinib)

97% Commercial Coverage

PBM, pharmacy benefit manager; GPO, group purchasing organization.
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

• 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

• 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 and durable response rates combined with the convenience of once-daily dosing

Coverage, reimbursement, and patient services

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

NSCLC, non-small cell lung cancer; RET, rearranged during transfection. \(^1\) Market Research conducted in Q2 2023 with 60 oncologists managing RET fusion-positive patients.
2024 Commercialization Timeline

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
TAVALISSE and REZLIDHIA 2023 Results
Growing Annual Sales of TAVALISSE and REZLIDHIA

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
Kinase inhibitor indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (cITP) who have had an insufficient response to a previous treatment.

Select Important Safety Information

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.
Creating Opportunities to Gain Market Share

81,300 U.S. Adult cITP Patients

<table>
<thead>
<tr>
<th>Line</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful Waiting</td>
<td>37,000</td>
</tr>
<tr>
<td>1st Line</td>
<td>20,000</td>
</tr>
<tr>
<td>2nd Line</td>
<td>11,400</td>
</tr>
<tr>
<td>3rd Line</td>
<td>6,900</td>
</tr>
<tr>
<td>4th Line</td>
<td>3,500</td>
</tr>
<tr>
<td>5L+</td>
<td>2,500</td>
</tr>
</tbody>
</table>

~75% of Post-Steroid Market

44,300 Patients Actively Treated
- 24,300 patients are 2L or later

Patient Moving through Therapies Creates New Patient Opportunities

TAVALISSE is Now Preferred on Key Commercial National Formularies
- Significant national commercial coverage
- Reinforces TAVALISSE’s proven efficacy and safety
- Strengthens reimbursement confidence
- Spreading awareness among customers through personal and non-personal channels

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cITP, chronic immune thrombocytopenia. 1. Symphony Health; PatientSource®, 10 years ending September 2019; 2. Internal market research conducted in October 2020. Please see Important Safety Information on slide 50. Please visit www.TAVALISSE.com for full prescribing information.
Promotion Efforts Highlight Data Supporting Use in Earlier Lines

Post-hoc Data Analysis Demonstrated Use as 2nd-Line Therapy Resulted in Higher Response Rates\(^1,2\)

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Response ≥ 50 x 10⁹/L</th>
<th>Response ≥ 30 x 10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd line (n=32)</td>
<td>94%</td>
<td>78%</td>
</tr>
<tr>
<td>3rd line (n=42)</td>
<td>86%</td>
<td>64%</td>
</tr>
<tr>
<td>4th line (n=27)</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>5th line (n=14)</td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td>All lines (n=145)</td>
<td>70%</td>
<td>54%</td>
</tr>
</tbody>
</table>

Durable Efficacy was Observed in Responders to TAVALISSE in the FIT Studies (combined results from FIT-1, FIT-2, and FIT-3)\(^3\)

Median Platelet Counts Over Time

**Post-hoc Data Analysis Demonstrated Use as 2nd-Line Therapy Resulted in Higher Response Rates**

2. Percentage of Patients Achieving Target Platelet Counts at Any Visit.  
TAVALISSE Q4 2023 Performance

2,463 Bottles Shipped to Patients and Clinics in Q4 2023

12% Growth Versus Q4 2022

$25.7M Q4 2023 Net Product Sales

Sales grew $3.8M (17%) vs Q4 2022

Growth Versus Q4 2022

Sales grew $3.8M (17%) vs Q4 2022

$25.7M Q4 2023 Net Product Sales

Bottles Shipped to Patients and Clinics

Q1 2019  Q2 2019  Q3 2019  Q4 2019
Q1 2020  Q2 2020  Q3 2020  Q4 2020
Q1 2021  Q2 2021  Q3 2021  Q4 2021
Q1 2022  Q2 2022  Q3 2022  Q4 2022
Q1 2023  Q2 2023  Q3 2023  Q4 2023

Q1 2019  Q2 2019  Q3 2019  Q4 2019
Q1 2020  Q2 2020  Q3 2020  Q4 2020
Q1 2021  Q2 2021  Q3 2021  Q4 2021
Q1 2022  Q2 2022  Q3 2022  Q4 2022
Q1 2023  Q2 2023  Q3 2023  Q4 2023

25
New Patient Starts Drove Growth in 2023

Consistent Quarterly Progress since Q2 2021

12% Compounded Annual Growth Rate (CAGR)

Total New Patient Starts

2020  2021  2022  2023
Expanding Access in Global Markets

In April 2023, Kissei launched TAVALISSE in Japan for the treatment of chronic ITP.

TAVALISSE is also commercially available in key European countries (TAVLESSE), Canada and Israel.
REZLIDHIA is 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.

Please see Important Safety Information on slides 51 & 52, including Boxed WARNING regarding differentiation syndrome.
mIDH1 Relapsed/Refractory AML Background

- AML is an aggressive, highly complex malignancy typically diagnosed in older adults.
- AML will be diagnosed in over 20K patients and result in nearly 11.2K deaths in 2024.
- IDH1 mutations are found in 6-9% of AML.
- mIDH1 patients are well-identified, and have limited options for treatment, particularly in relapsed/refractory (R/R) disease.
- A significant unmet need exists for targeted treatments for mIDH1 R/R AML that are well-tolerated and efficacious.

IDH1, isocitrate dehydrogenase-1; mIDH1, mutated IDH1; R/R, relapsed or refractory; AML, acute myeloid leukemia.
REZLIDHIA Phase 2 Clinical Trial: Study Design

**Monotherapy**
REZLIDHIA² 150 mg BID

- **Cohort 1:** R/R AML (N=153)
- **Cohort 2:** AML in CR/CRi but MRD positive
- **Cohort 3:** R/R AML/MDS treated previously with IDH1 inhibitor therapy AND standard treatments are contraindicated
- **Cohort 7:** TN AML for whom standard treatments are contraindicated

**Combination Therapy**
REZLIDHIA² 150 mg BID + AZA³

- **Cohort 4:** R/R AML/MDS naïve to prior HMA and IDH1 inhibitor therapy
- **Cohort 5:** R/R AML/MDS inadequately responded to or progressed on prior HMA
- **Cohort 6:** R/R AML/MDS treated previously with IDH1 inhibitor monotherapy as last prior therapy
- **Cohort 8:** TN AML candidates for AZA as first-line treatment

**Primary Endpoint:**
- CR+CRh rate

**Key Secondary Endpoints:**
- ORR, DOR, Transfusion independence, OS
- Safety

**Cohort 1:** All adults, median age 71 (32-87) years, 73% had intermediate AML cytogenetic risk. Most (75%) had ≥1 co-occurring mutations. Most (97%) had prior induction therapy and a median 2 (1-7) prior treatments (all naïve to m1DHI-inhibitor).

IDH1, isocitrate dehydrogenase-1; mIDH1, mutated IDH1; R/R, relapsed or refractory; AML, acute myeloid leukemia; BID, twice daily; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete count recovery; MRD, minimal residual disease; HMA, hypomethylating agents; ORR, overall response rate; DOR, duration of response; OS, overall survival; AZA, azacitidine.

1. NCT02719574. 2. REZLIDHIA PO given daily over continuous 28-day cycles. 3. AZA IV or SC given daily on Days 1–7 of each 28-day cycle; patients received first dose >6 months prior to data cutoff of June 18, 2021. Source: Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 7006-7006 doi: 10.1200/JCO.2021.39.15_suppl.7006
REZLIDHIA Phase 2 Clinical Trial: Summary

- CR+CRh rate of 35%, with a median duration of response of 25.9 months
- 92% of CR+CRh responders were CR, with a median duration of response of 28.1 months
- Transfusion independence was achieved in all subgroups
- REZLIDHIA has a well characterized safety profile with no cardiac events leading to discontinuation
REZLIDHIA Q4 2023 Performance

278 Bottles Shipped to Patients and Clinics in Q4 2023

$3.9M Q4 2023 Net Product Sales

$11.4M Launch Sales To-Date
Driving Continued Growth

Promotional Activities

Institutional Team Fully Deployed:
• Leading REZLIDHIA promotional activities with top leukemia treaters and facilitating formulary placement at key AML accounts
• Continued progress with key institutions and leukemia treaters in Q4 2023, with numerous engagements at ASH

Other Key Activities:
• Speaker programs
• Leukemia and hematology conferences
• Increase REZLIDHIA awareness upon diagnosis
• Continue to maximize access for patients

Scientific Activities

Additional Phase 2 Publications
• Key mIDH1 R/R patient populations (i.e. post Venetoclax)
• Other key populations from non-pivotal cohorts (i.e. MDS)

Supportive Data Generation
• Bolster available data in important, difficult-to-treat mIDH1 R/R patient populations through Real World Evidence

Other Key Activities
• Providing relevant scientific information and education for HCPs
• Gathering insights from KOLs to better understand how to develop olutasidenib

IDH1, isocitrate dehydrogenase-1; mIDH1, mutated IDH1; R/R, relapsed or refractory; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; HCPs, healthcare professionals; KOLs, key opinion leaders. Please see Important Safety Information on slides 51 & 52. Please visit www.REZLIDHIA.com for Full Prescribing Information, including Boxed WARNING.
Development Programs Update
Hematology and Oncology Pipeline Expansion

**Development Opportunities**

- **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

**In-Licensing & Product Acquisition**

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

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IDH1, isocitrate dehydrogenase-1; miDH1, mutated IDH1; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; IRAK1/4, interleukin receptor-associated kinases 1 and 4.

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

- 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
Gliomas account for 29-35% of the CNS tumors in pediatric, adolescents and young adult patients, with approximately 1/3 being high grade gliomas (HGG) (800-1000 new cases/year)\(^1\)

Overall IDH1 mutations are found in 6% of pediatric HGG and up to 36% of HGGs in adolescents and young adult\(^2,3,4\)

**Pediatric/AYA Glioma Treatment Landscape**

- Newly diagnosed high grade glioma
  - Treatment includes maximal safe surgical resection, standard radiation therapy and adjuvant temozolomide

- Recurrent or progressive disease
  - Diffuse or multiple ➔ systemic therapy or surgery for symptomatic large lesions
  - Local ➔ resection ➔ brain MRI ➔ clinical trials or systemic therapy

- Palliative/best supportive care

HGGs are a leading cause of cancer-related death in children and adolescents. Despite intensive multimodal therapy, prognosis for pediatric, adolescent, and young adult patients diagnosed each year in the U.S. with HGG remain dismal, with 5-year overall survival (OS) <10%\(^5,6\)

AYA, adolescent and young adult; CNS, central nervous system; HGG, high-grade glioma; IDH1, isocitrate dehydrogenase-1; MRI, magnetic resonance imaging; OS, overall survival.

1. Epidemiology, diagnosis, and optimal management of glioma in adolescents and young adults, Tejjan P. Diwanji et al, Adolesc Health Med Ther 2017; 8:99-113
Collaboration with CONNECT to Conduct a Phase 2 Trial of Olutasidenib in Glioma

- 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.

IDH1, isocitrate dehydrogenase-1; HGG, high-grade glioma.
1. Investigational compound in this indication and not approved by the FDA.
CONNECT Phase 2 Clinical Study Design

Olutasidenib in combination with temozolomide (TMZ) followed by olutasidenib monotherapy as maintenance treatment in newly diagnosed pediatric and young adult patients (<39 years) with IDH1 mutation positive HGG

Primary objectives:
• Assess safety and tolerability of olutasidenib in pediatric patients
• Estimated progression-free survival vs historical controls
• Characterize PK properties of olutasidenib in pediatric patients

Multiple secondary objectives include:
• Evaluate the radiographic objective response rate and health-related quality of life outcomes
• Overall survival vs historical controls

Initiation:
• Estimated in the first half of 2024

IDH1, isocitrate dehydrogenase-1; HGG, high-grade glioma; PO, orally; BID, twice daily; QD, once daily; PK, pharmacokinetics.

1. Investigational compound in this indication and not approved by the FDA.
Targeting IRAK1 & IRAK4 Pathways in Heme/Onc

R289/835 is a Dual Inhibitor of Both IRAK1 and IRAK4 Pathways

• Inhibition of IRAK1/4 kinases has therapeutic potential for multiple diseases
• In a preclinical study, dual Inhibition of IRAK1 & IRAK4 demonstrated greater suppression of inflammatory cytokines compared to an IRAK4-selective inhibitor

Attractive Opportunities in Heme/Onc and Rare Immune Diseases Align with Development Strategy

• Activation of innate immune system through TLRs and IL-1Rs plays an important role in myelodysplastic syndrome (MDS) pathogenesis
• The downstream IRAK1/4 signaling network mediates NLRP3 inflammasome-driven pyroptosis, which drives bone marrow inflammation in lower-risk MDS
• The first patients dosed in an open-label, Phase 1b clinical trial of study in lower-risk MDS. The primary endpoint for this trial is safety with key secondary endpoints including preliminary efficacy

Targeting IRAK1 & IRAK4 Pathways in Inflammatory Disease

Dual Inhibition of IRAK1 and IRAK4 Provides Stronger Suppression of Inflammatory Cytokines Compared to IRAK4-selective Inhibitor

**Kinase Assays**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>IRAK4</th>
<th>IRAK1</th>
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<tr>
<td>Substrate</td>
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**IRAK4-Selective Inhibitor**

<table>
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<tr>
<th>Assay</th>
<th>Rigel Data on File</th>
<th>R835 IC50</th>
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<tbody>
<tr>
<td>IL-1b Huvec IL-6</td>
<td>100% Inhibition</td>
<td>IRAK4 IC50 = 15nM</td>
</tr>
<tr>
<td>IL-1b Huvec IL-6</td>
<td>100% Inhibition</td>
<td>IRAK1 IC50 = 14nM</td>
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**IRAK1/ IRAK4 Dual Inhibitor**

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</tr>
</tbody>
</table>

IRAK1/4, interleukin receptor-associated kinases 1 and 4; TLR, toll-like receptor; IL, interleukin; LPS, lipopolysaccharide.

1. R835 is an investigational compound not approved by the FDA. 2. Rigel data on file.
R835\textsuperscript{1} Proof-of-Mechanism and First-in-Human Studies\textsuperscript{3}

**Cytokine Response After LPS Challenge**

**Proof-of-Mechanism**

In LPS\textsuperscript{2} Challenge study in healthy volunteers, R835 profoundly inhibited inflammatory cytokine production\textsuperscript{2}:
- Inhibited TNF\(\alpha\), IL-6, and IL-8

**First-in-Human**

First-In-Human study enrolled 82 adults to characterize the safety, PK, PD of R835:
- R835 was well tolerated
- Linear PK profile and dose proportional exposure

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LPS, lipopolysaccharides; TNF\(\alpha\), tumor necrosis factor-\(\alpha\); IL, interleukin; PK, pharmacokinetics; PD, pharmacodynamics; LPS, lipopolysaccharide.

1. R835 is an investigational compound not approved by the FDA.
2. Lipopolysaccharide (LPS, a TLR4 agonist).
Lower-Risk MDS Treatment Landscape

- MDS is a clonal disorder of hematopoietic stem cells (HSCs) leading to dysplasia and ineffective hematopoiesis in the bone marrow
- Risk of autoimmune abnormalities, cytopenias, progression to AML and death

1. First-Line Therapy: Transfusions and ESAs
   Treatment includes frequent blood transfusions and Erythropoiesis-Stimulating Agents (ESAs) for anemia

2. Second-Line Therapy: Lenalidomide, Luspatercept, Hypomethylating Agents (HMAs),
   and immunosuppressive therapy provide limited hematologic response in selected subsets of patients, durable responses are not common, and these agents can result in significant adverse effects

X. Loss of Response
   is associated with significant morbidity and cytopenias

There are currently no standard therapies for lower-risk MDS patients who are refractory/resistant to current second-line therapies

MDS, myelodysplastic syndrome; HSCs, hematopoietic stem cells; AML, acute myeloid leukemia; ESAs, erythropoiesis-stimulating agents; HMAs, hypomethylating agents.
Bone Marrow Failure in Low Risk MDS is Driven by Chronic Inflammation and Pyroptosis of Normal Hematopoietic Stem Cells


MDS, myelodysplastic syndrome; IRAK1/4, interleukin receptor-associated kinases 1 and 4; HSC, hematopoietic stem cell; TLR, toll-like receptor; TNF, tumor necrosis factor-α; IL, interleukin; Myd88, myeloid differentiation primary response 88; HMGB1, high mobility group box-1 protein; DAMPs, damage-associated molecular patterns.
R289 Development: Open-label Phase 1b Study of Patients with Lower-Risk MDS

Patients with Lower-Risk MDS
Relapsed/Refractory or Inadequate Response to Prior Therapy with Known Clinical Benefit*

Primary Endpoint:
- Safety

Secondary Endpoints:
- Preliminary Efficacy
  - Transfusion Independence
  - Remission
  - Overall Response
  - Hematologic Improvement
- PK
- Biomarkers

MDS, myelodysplastic syndrome; PK, pharmacokinetics.

*Thrombopoietin (TPO), erythropoietin (EPA), luspatercept, and hypomethylating agents (HMAs) [i.e., azacytidine or decitabine]. Patients with del (5q) must have failed prior lenalidomide therapy.

1. Investigational compound not approved by the FDA.
RIPK1 Inhibitor Programs in Immune and CNS Diseases with Partner Lilly

**Immune Diseases**
- R552, a potent and selective RIPK1 inhibitor, completed a Phase 1 study which demonstrated potential best-in-class status compared to competition.
- Lilly initiated a Phase 2a clinical trial studying LY3871801 (previously R552) in adult patients with moderately to severely active rheumatoid arthritis.

**CNS Diseases**
- Selection of RIPK1 inhibitor candidates that cross the blood-brain barrier for CNS diseases is underway.
- Lilly would lead clinical development of brain-penetrating RIPK1 inhibitors in CNS diseases.

RIPK1 inhibitors play key role in TNF signaling and induction of pro-inflammatory necroptosis, which could support broad potential in RA, psoriasis and IBD, and with their experience, Lilly is the ideal partner.
Financials
Q4 2023 Financial Highlights

Total Revenue: $35.8M
- Net Product Sales: $29.5M
  - TAVALISSE: $25.7M
  - REZLIDHIA: $3.9M
- Contract revenues from collaborations: $6.2M
  - Grifols $3.7M
  - Kissei $2.2M
  - Medison $0.3M
- Government contract revenue: $0.1M

Total Bottles Shipped:
- TAVALISSE: 2,671
- REZLIDHIA: 308

Bottles Shipped to Patients and Clinics¹:
- TAVALISSE: 2,463
- REZLIDHIA: 278

Cash, cash equivalents & short-term investment as of December 31, 2023 was $56.9M as of December 31, 2022 compared to $58.2M as of December 31, 2022.
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 Programs¹
• 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

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

¹ Investigational compounds in these indications and not approved by the FDA. Please see Important Safety Information on slides 50-54. 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 may be required.
- 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/](http://www.tavalisse.com/) for full Prescribing Information

To report side effects of prescription drugs to the FDA, visit [http://www.fda.gov/medwatch](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/pleuroperticardial 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/pleuroperticardial effusion, kidney injury, 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.
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.