Rigel Corporate Presentation

June 16, 2026

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, the anticipated benefits of the transaction with Arvinas, Inc. and Pfizer Inc., the associated license agreement, the potential of VEPPANU (vepdegestrant), Rigel's expectations regarding the commercialization, market opportunity and potential contribution of VEPPANU to its commercial portfolio and future growth, continued development and expansion of our business, projected financial performance, including sales and revenue growth, continued advancement of our R289 study, expanded indications for olutasidenib alone or in combination with other agents, potential identification of opportunities and completion of acquisitions or in-license of complementary late-stage assets, efficacy of products in clinical trials and related future performance, potential clinical benefit and market opportunity for our commercial portfolio, ability to complete clinical studies on schedule, regulatory agency approvals in other markets or indications for vepdegestrant, fostamatinib or olutasidenib, pralsetinib or R289, success of our partnering efforts including business growth and financial and commercial milestone achievements, and Rigel's ability to achieve the projected 2026 financial outlook and future growth objectives.

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", "outlook", "anticipates", "expects", "will", "promising" 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 related to the anticipated benefits of the license agreement or the commercialization of VEPPANU not being realized; risks related to the transfer of development, manufacturing and commercialization responsibilities to Rigel, including risks associated with integrating newly acquired or licensed assets; risks related to Rigel's dependence on third parties, including Arvinas and Pfizer, for development, manufacturing and supply activities; anticipated financial performance for 2026; anticipated timing and results from the clinical development of R289; Rigel's intention to fund existing and new clinical development programs while anticipating positive net income for 2026; our growth strategy and anticipated financial and operational performance for 2026 and beyond, including that growth rates or trajectory assumptions may not materialize; risks and uncertainties associated with the commercialization and marketing of VEPPANU, TAVALISSE, GAVRETO, and REZLIDHIA; risks that the FDA, European Medicines Agency, PMDA or other regulatory authorities may make adverse decisions regarding VEPPANU, TAVALISSE, GAVRETO, REZLIDHIA or R289; operational, development, regulatory or other risks that can affect the timing of enrollment and data availability for R289 clinical development; risks that clinical trials may not be predictive of real-world results or of results in subsequent clinical trials; risks that VEPPANU, TAVALISSE, GAVRETO, REZLIDHIA or R289 may have unintended side effects, adverse reactions or incidents of misuse; the availability of resources to develop or market Rigel's product candidates; market competition; unanticipated business needs and other developments, including potential partnering, licensing or other collaboration arrangements, which could impact Rigel's funding needs or other internal resource demands, as well as other risks detailed from time to time in Rigel's reports filed with the Securities and Exchange Commission, including its Quarterly Report on Form 10-Q for the quarter ended March 31, 2026 and subsequent filings.

Any forward-looking statement in this presentation 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's Transformational Growth Strategy

Grow Commercial Business

In-Licensing / Business Development

Maintain Financial Discipline

Advance Development Pipeline

Rigel's Transformational Growth Strategy

Grow Commercial Business

In-Licensing / Business Development

Maintain Financial Discipline

Advance Development Pipeline

2020

- One commercial product
- Limited development pipeline

2025

- Three commercial products
- Development pipeline opportunity advancement, including R289 in lower-risk MDS
- Profitable since Q3 2024; $100+ million increase in cash through end of 2025[1]

2030s

- Growth of four commercial products
- Growth from potential in-licensing / M&A transactions
- Transformational development pipeline, including R289 portfolio and other potential opportunities[2]

MDS, myelodysplastic syndrome.

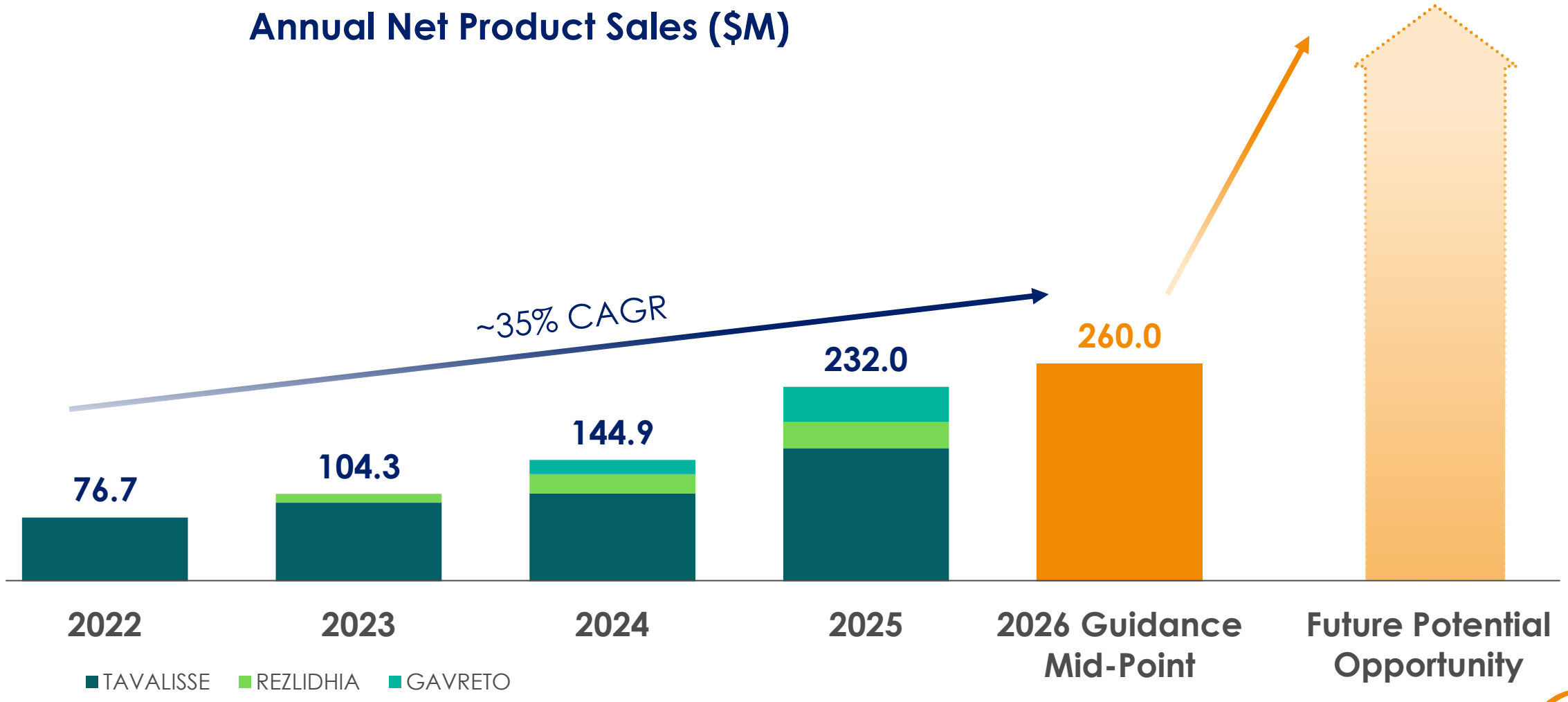
1. Cash, cash equivalents & short-term investments balance was $49.1 million as of 6/30/24 and $155.0 million as of 12/31/25. **2.** Investigational compounds in these indications and not approved by the FDA.

Rigel Announces In-License of VEPPANU™ (vepdegestrant) for the Treatment of 2L+ *ESR1*m ER+/HER2- MBC

- On May 12, 2026, Rigel announced it entered into an exclusive, global license agreement with Arvinas and Pfizer to develop, manufacture and commercialize VEPPANU™ (vepdegestrant), the first and only FDA-approved oral PROteolysis TArgeting Chimera (PROTAC)
- VEPPANU was approved by the FDA on May 1, 2026, for the treatment of adults with ER+/HER2-, *ESR1*-mutated advanced or metastatic breast cancer, as detected by an FDA-authorized test, with disease progression following at least one line of endocrine therapy
- Following the effective date, Arvinas and Pfizer have received an upfront payment of $70.0 million and will receive an additional $15 million in transition payments. Arvinas and Pfizer are also eligible to receive up to $320.0 million in future potential regulatory and commercial milestones
- VEPPANU is Rigel's fourth commercial product and is expected to contribute meaningfully to the advancement of Rigel's transformational growth strategy

2L, second line; 2L+, second line-plus; ESR1, estrogen receptor 1 gene; ESR1m, ESR1 mutated; ER+/HER2-, estrogen receptor-positive, human epidermal growth factor receptor 2-negative; MCS, metastatic breast cancer; FDA, U.S. Food and Drug Administration.

Future Transformational Revenue Growth Opportunities



CAGR, compound annual growth rate.

Note: 2026 guidance mid-point is as of May 5, 2026 and does not include vepdegestrant in-licensing transaction.

Grow Commercial Business

Q1 2026 Commercial Performance

Net Portfolio Sales grew $11.3M (26%) vs. Q1 2025

Tavalisse® (fostamatinib disodium hexahydrate) tablets

$37.3M
Q1 2026 Net Product Sales

31%
Growth vs. Q1 2025

GAVRETO® pralsetinib 100mg capsules

$9.6M
Q1 2026 Net Product Sales

7%
Growth vs. Q1 2025

REZLIDHIA® (olutasidenib) 150 mg capsules

$8.0M
Q1 2026 Net Product Sales

31%
Growth vs. Q1 2025

Tavalisse®
(fostamatinib disodium hexahydrate) tablets

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.

Please see Important Safety Information on slide 59. Please visit www.TAVALISSE.com for Full Prescribing Information.

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Creating Opportunities to Gain Market Share

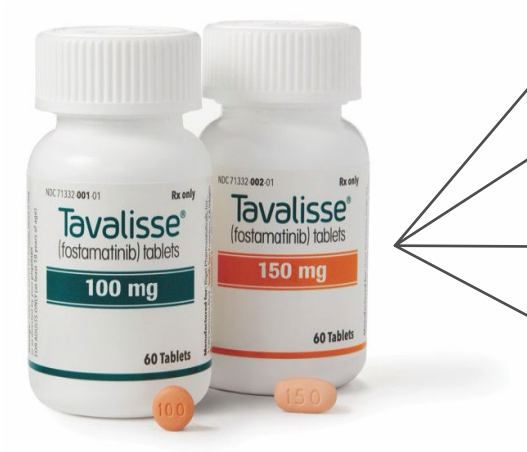
Tavalisse® (fostamatinib disodium hexahydrate) tablets

81,300 U.S. Adult cITP Patients[1]

37,000
Watchful Waiting

20,000
1st Line

11,400
2nd Line



6,900
3rd Line

3,500
4th Line

2,500
5L+

44,300 Patients Actively Treated[2]

- 24,300 patients are 2L or later

Patients Need Additional Treatment Options as They Move through Therapies

Significant National Commercial Coverage

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 59. Please visit www.TAVALISSE.com for full prescribing information.

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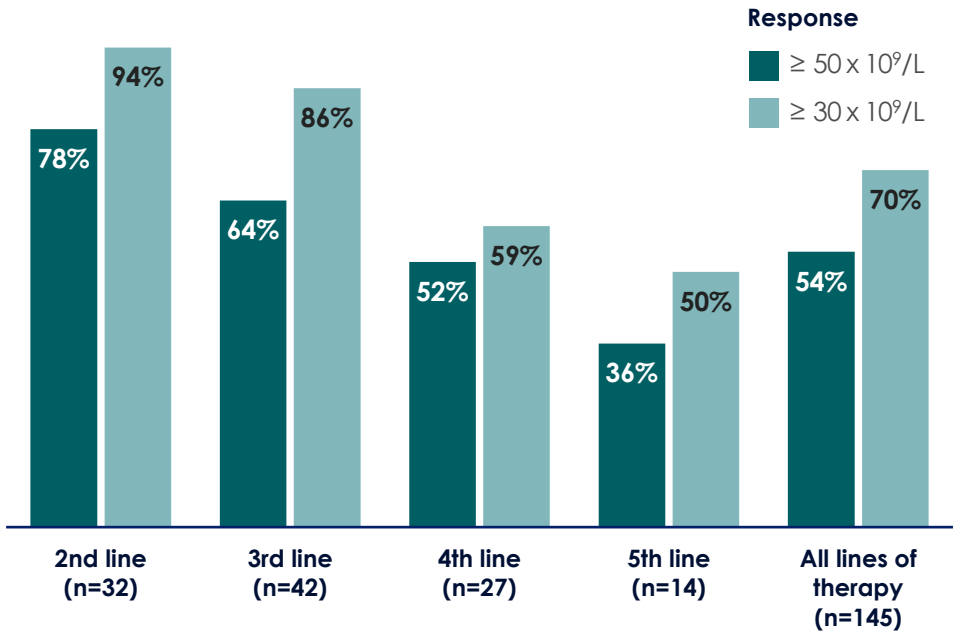
Efficacy Across All Post-Steroid Lines of Therapy

Tavalisse® (fostamatinib disodium hexahydrate) tablets

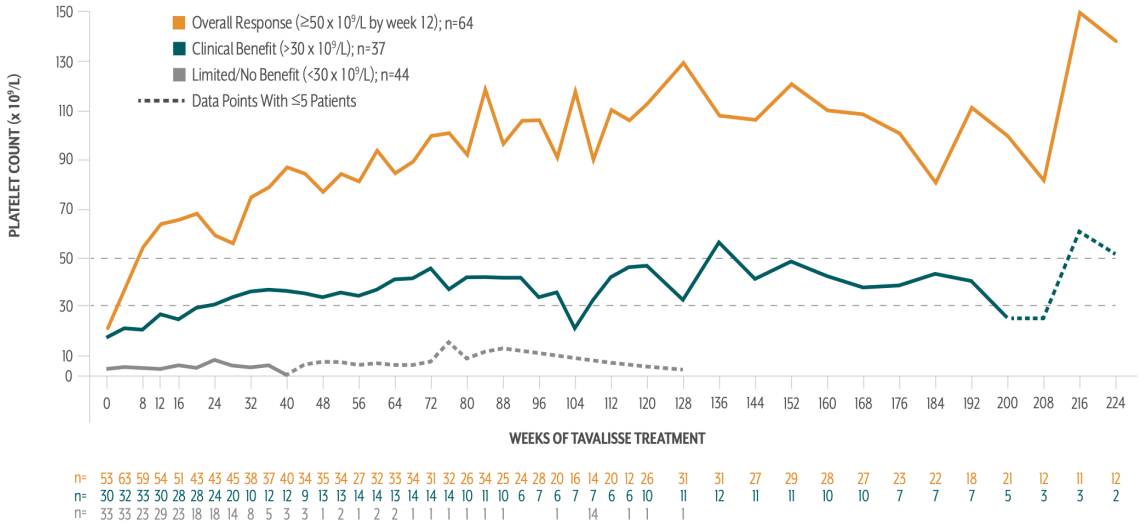
Post-hoc Data Analysis Demonstrated Use as 2nd-Line Therapy Resulted in Higher Response Rates[1,2]



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



FIT, Fostamatinib in ITP

1. Fostamatinib is an effective 2nd-line therapy in patients with immune thrombocytopenia, British Journal of Haematology. **2.** Percentage of Patients Achieving Target Platelet Counts at Any Visit. **3.** Assessment of thrombotic risk during long-term treatment of immune thrombocytopenia with fostamatinib, Therapeutic Advances in Hematology, 4/30/21. Please see Important Safety Information on slide 59. Please visit www.TAVALISSE.com for Full Prescribing Information.

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REZLIDHIA® (olutasidenib) 150 mg capsules

APPROVED AND AVAILABLE IN THE U.S.

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 60 & 61, including Boxed WARNING regarding differentiation syndrome

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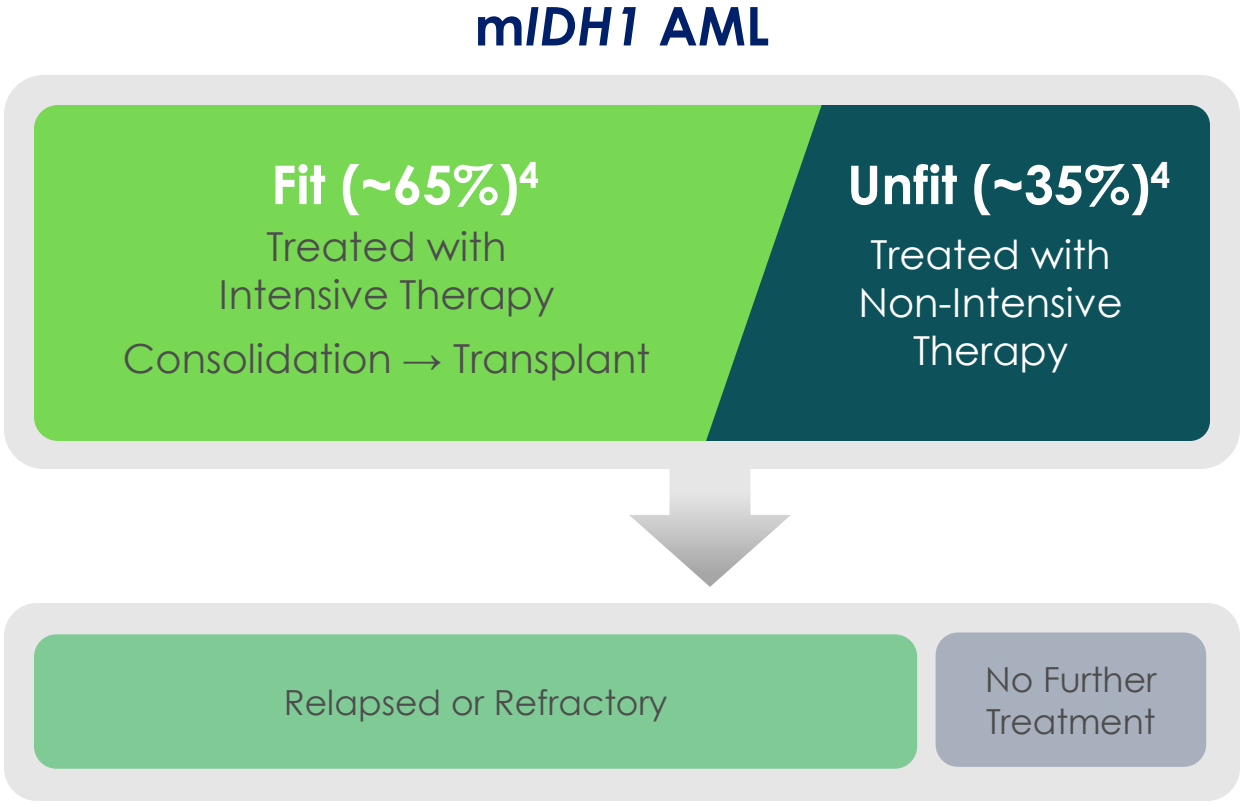
m*IDH1* Relapsed/Refractory AML Background

REZLIDHIA® (olutasidenib) 150 mg capsules

- AML will be diagnosed in nearly 23K patients and result in nearly 11.5K deaths in 2026[1]
- IDH1 mutations are found in 6-9%[2,3] of AML
- m*IDH1* 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 m*IDH1* R/R AML that are well-tolerated and efficacious



IDH1, isocitrate dehydrogenase-1; m*IDH1*, mutated IDH1; R/R, relapsed or refractory; AML, acute myeloid leukemia.

1. American Cancer Society, Key Statistics for Acute Myeloid Leukemia (AML). 2026. **2.** Abbas S et al. Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. Blood (2010) 116 (12): 2122-2126. **3.** Chotirat S et al. Molecular alterations of isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) metabolic genes and additional genetic mutations in newly diagnosed acute myeloid leukemia patients. J Hematol Oncol 5, 5 (2012). **4.** Rigel HCP Quantitative Market Research, 2022 (Data on File).

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REZLIDHIA Phase 2 Clinical Trial Highlights[1]

- Elderly population (median age 71) with a median of 2 (1-7) prior treatments (all naïve to m1DHI-inhibitor)
- CR+CRh rate of 35%, with a median duration of response of 25.3 months
- 92% of CR+CRh responders were CR, with a median duration of response of 25.3 months
- Transfusion independence was achieved in all subgroups
- REZLIDHIA has a well characterized safety profile with no cardiac events leading to discontinuation

BID, twice daily; R/R, relapsed or refractory; IDH1, isocitrate dehydrogenase-1; m*IDH1*, mutated IDH1; AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; ORR, overall response rate; DOR, duration of response, OS, overall survival.

1. Cortes, J., Curti, A., Fenaux, P. *et al.* Olutasidenib for mutated *IDH1* acute myeloid leukemia: final five-year results from the phase 2 pivotal cohort. *J Hematol Oncol* 18, 102 (2025).

APPROVED AND AVAILABLE 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 62 & 63, including Boxed WARNING regarding serious infections

* 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).

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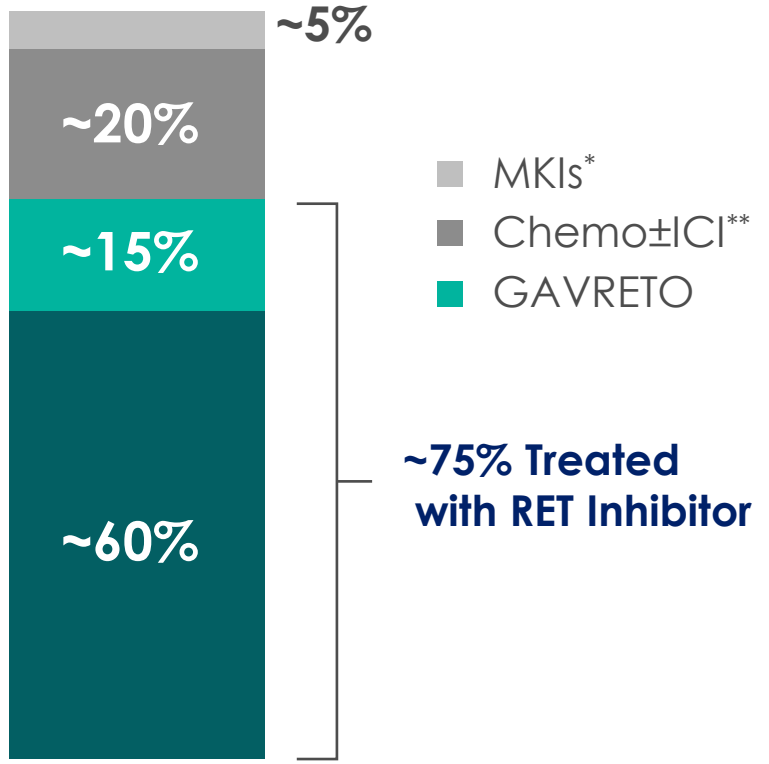
Growing Our Oncology Targeted Therapy Portfolio

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

1L Treatment of RET Fusion-Positive NSCLC Patients[1]



RET, rearranged during transfection; NSCLC, non-small cell lung cancer. 1. Market Research conducted in Q2 2023 with 60 oncologists managing RET fusion-positive patients; *Multi-Kinase Inhibitors; **Immune Checkpoint Inhibitors (anti PD-1/PD-L1)

Pralsetinib Has a Differentiated Value Proposition

- The **only once daily, oral,** RET inhibitor approved for patients with NSCLC and thyroid cancer with RET gene fusions
- **High and durable response rates** regardless of prior treatment history[1]
- Promising intracranial efficacy in patients with **brain metastases**[1]
- Established **safety and tolerability** profile
- NSCLC practice guidelines now **recommend as a preferred 1L treatment option for RET+ patients, including for patients identified during 1L treatment with systemic therapy**

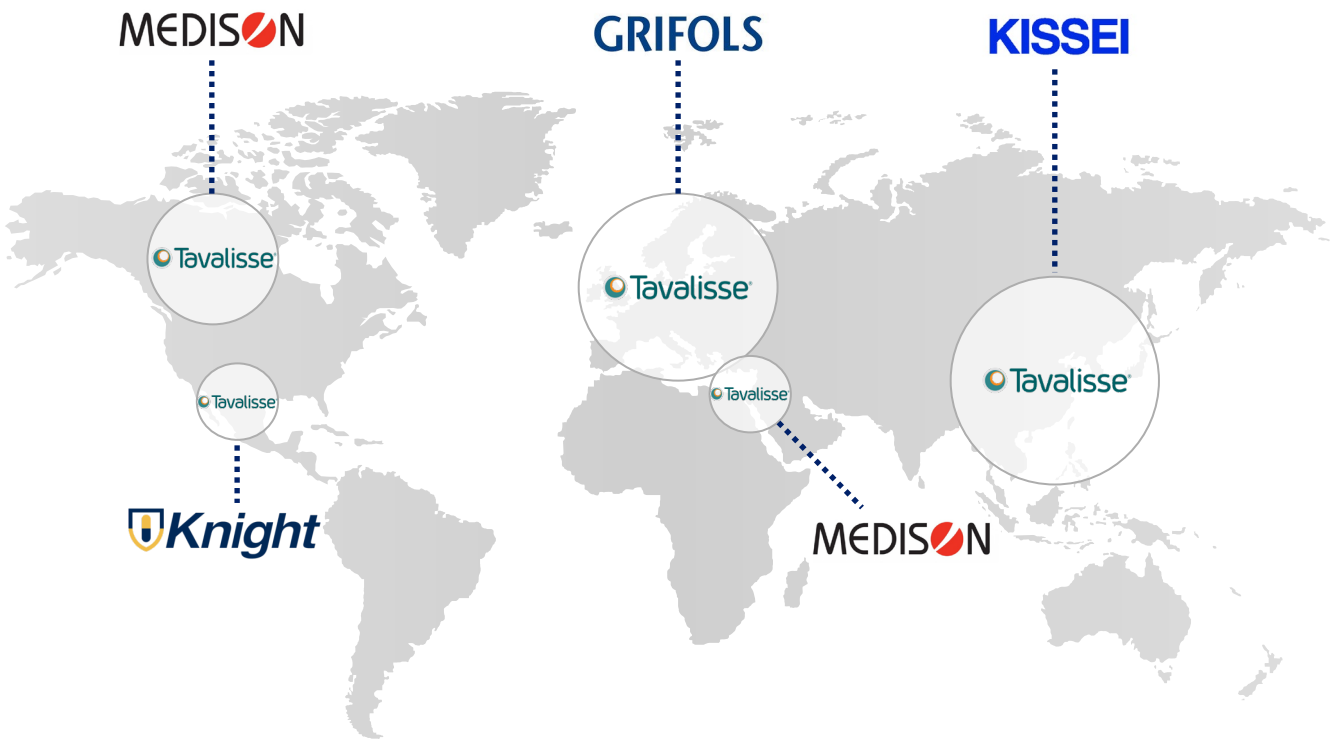
NSCLC, non-small cell lung cancer; RET, rearranged during transfection; 1L, first-line.

1. Besse B et al. Ann Oncol. 2022; 33(suppl 7). Please visit www.GAVRETO.com for Full Prescribing information, including Boxed WARNING.

Expanding Commercial Access Globally

Expanding Commercial Availability in Global Markets

TAVALISSE is commercially available in key European countries (TAVLESSE), Japan, South Korea, Canada and Israel



Q1 2026 Collaboration Revenues

- Grifols $1.8M
- Kissei $1.8M
- Medison $0.3M

TAVALISSE Commercial Launch

- Knight announced launch of TAVALISSE in Mexico in May

TAVALISSE Regulatory Approval

- Knight announced regulatory approval in Brazil in May

REZLIDHIA Opportunity[1]

- Executing on ex-U.S. opportunities for development and commercialization
  - Expanded relationship with Kissei to include REZLIDHIA in Japan, South Korea, and Taiwan
    - Kissei submitted NDA in Japan in May
  - Entered relationship with Dr. Reddy's in Latin America and other territories[2]

NDA, New Drug Application.
1. Forma, now Novo Nordisk, is entitled to a certain portion of Rigel's sublicensing revenue from olutasidenib.
2. Dr. Reddy's territory includes Latin America, South Africa, certain countries in the Commonwealth of Independent States (CIS), India, certain countries in Southeast Asia and North Africa, Australia and New Zealand.

In-Licensing / Business Development

In-Licensing / Business Development Strategy

Differentiated asset(s) in hematology, oncology or related areas

- Acquired global rights to REZLIDHIA in 2022; first commercial sale in patients with R/R m*IDH1* AML in Q4 2022
- Acquired U.S. rights to GAVRETO in 2024; first commercial sale in patients with *RET*+ NSCLC and thyroid cancer in Q3 2024
- Acquired global rights to VEPPANU in June 2026; FDA approved for the treatment of 2L+ ER+/HER2-, *ESR1*m mBC on May 1, 2026

Late-stage programs

- Seeking assets that have completed registrational trial
- Assets ready for NDA filing, NDA filing is in process / under review with FDA or product is currently commercially available

Synergistic to current in-house capabilities and capacity

- Leverage existing commercial and operating infrastructure
- Rapid accretion, increased cash flows, and enhanced business value

R/R, relapsed or refractory; IDH1, isocitrate dehydrogenase-1; mIDH1, mutated IDH1; AML, acute myeloid leukemia; RET, rearranged during transfection; RET+, RET-fusion positive; NSCLC, non-small cell lung cancer; NDA, new drug application; FDA, U.S. Food and Drug Administration; ER+/HER2-, estrogen receptor-positive, human epidermal growth factor receptor 2-negative; ESR1, estrogen receptor 1 gene; ESR1m, ESR1 mutated; mBC, metastatic breast cancer.

VEPPANU™ (vepdegestrant) In-License Agreement

VEPPANU has the Potential to Transform Rigel's Commercial Portfolio

VEPPANU (vepdegestrant) is the **first and only FDA-approved PROTAC**, a new class of targeted agents

Vepdegestrant has a **novel and unique mechanism of action** and has the **potential to be an important new therapy** for 2L and 3L ER+/HER2-, *ESR1*m metastatic breast cancer

Rigel's proven commercial and medical infrastructure and expertise will **enable us to successfully launch** VEPPANU

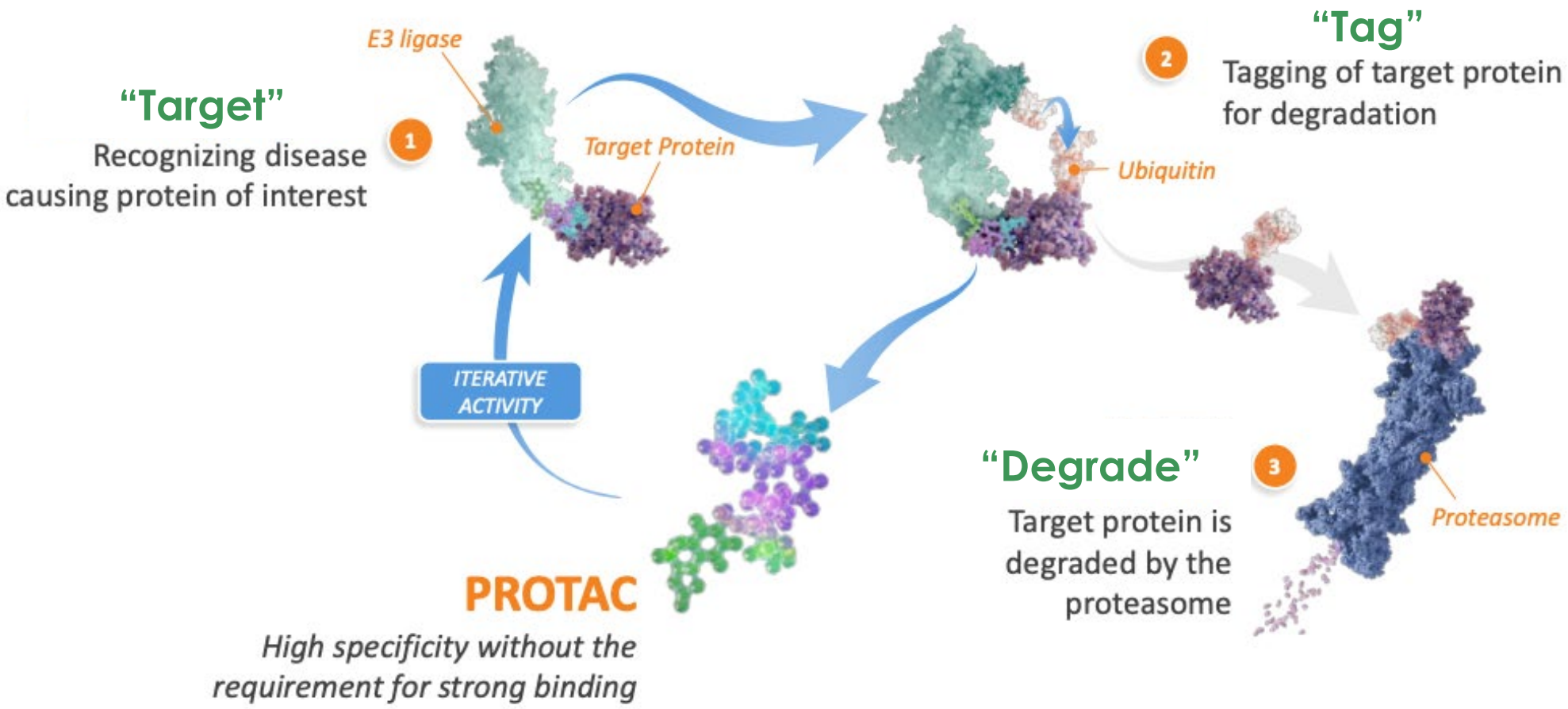
VEPPANU has the **potential to become Rigel's largest revenue producer**

FDA, U.S. Food and Drug Administration; PROTAC, PROteolysis TArgeting Chimera degrader; 2L, second line; 3L, third line; ER+/HER2-, estrogen receptor-positive, human epidermal growth factor receptor 2-negative; ESR1, estrogen receptor 1 gene; ESR1m, ESR1 mutated.

Vepdegestrant MOA and Differentiation

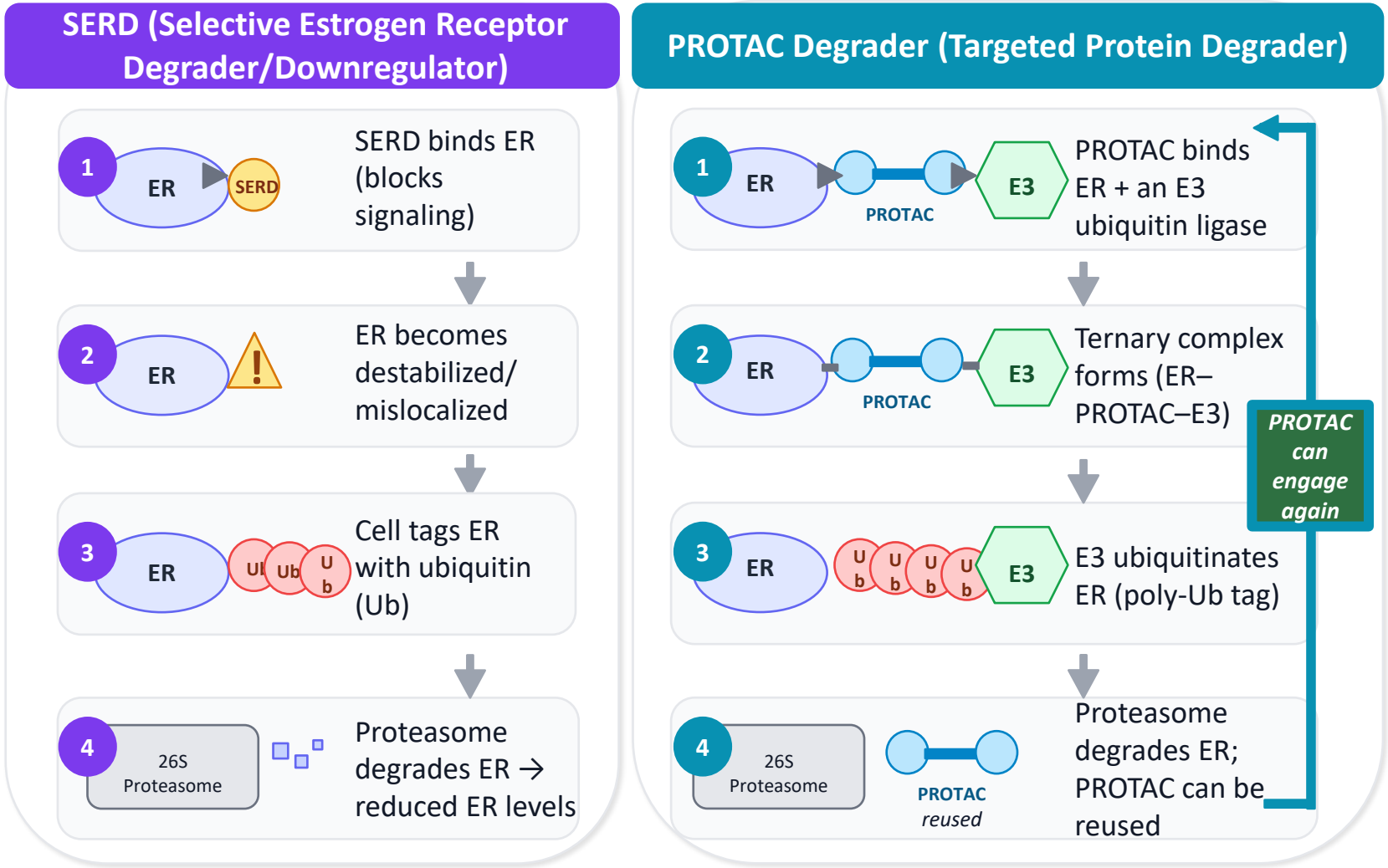
PROteolysis TArgeting Chimera (PROTAC):

Targeting disease-causing proteins for degradation and disposal



PROTAC Degraders Are Differentiated From SERDs

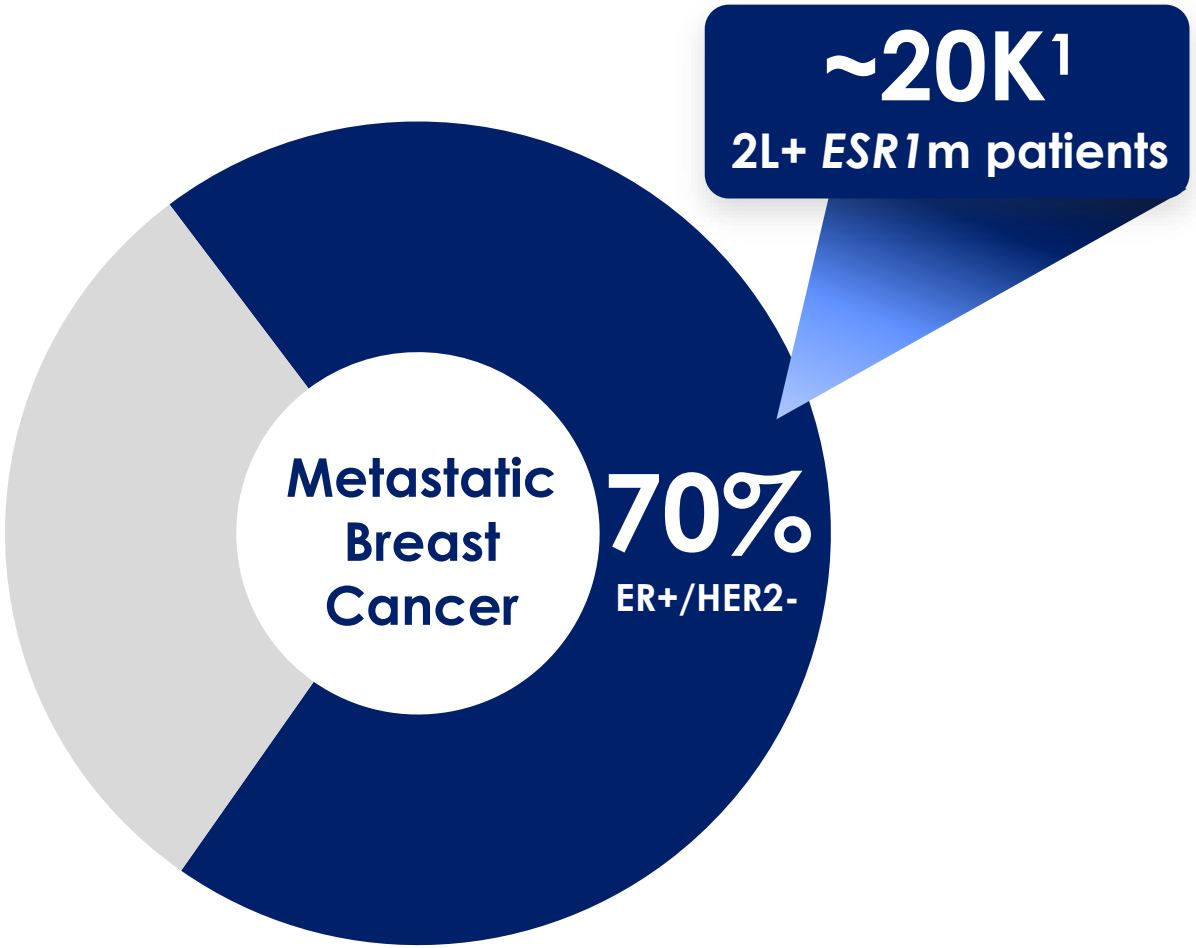
- SERDs bind to the estrogen receptor (ER), destabilizing the ER, making it more prone to degradation
- PROTACs specifically target the estrogen receptor, marking it for selective destruction by the cell
  - PROTAC is released for further ER targeting
- While 1 SERD molecule binds one ER, 1 PROTAC molecule can destroy many receptors



Legend: Ub = ubiquitin tag • E3 = ubiquitin ligase • 26S proteasome = protein degradation machine

Vepdegestrant Addresses Significant Unmet Medical Need

Rigel is Entering a Major Oncology Market with a High Unmet Need



$1B+ US Market Opportunity

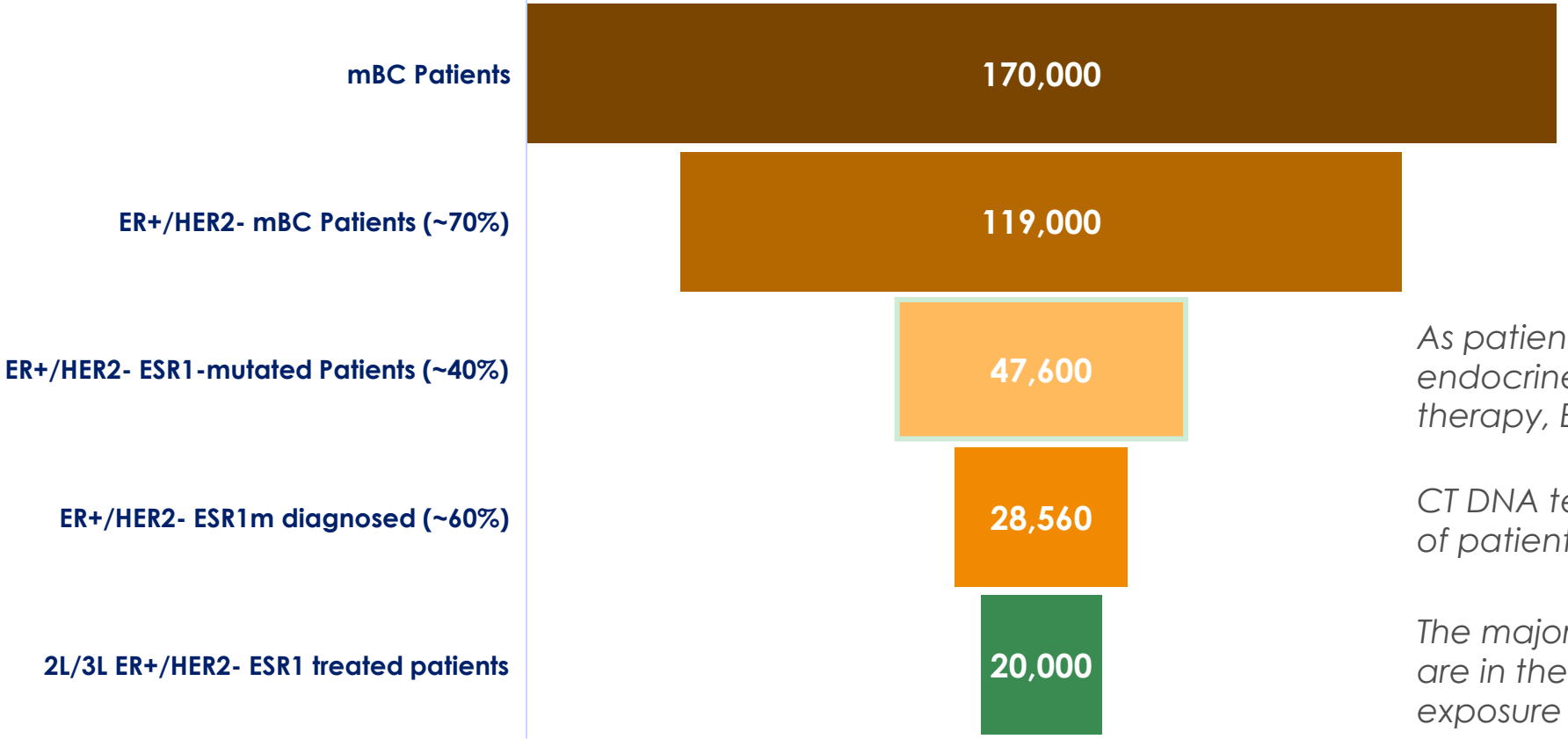
- **ER+/HER2- patient population represents the majority (70%) of breast cancer**, where treatment with endocrine therapies (AIs) is the SOC
- **Up to 50% of patients acquire an *ESR1* mutation following** exposure to an endocrine therapy
- **This creates a very sizable population of approximately 20,000 2L/3L ER+/HER2-, *ESR1*m mBC patients**, who need new options to treat their disease

ER+/HER2-, estrogen receptor-positive, human epidermal growth factor receptor 2-negative; SOC, standard of care; ESR1, estrogen receptor 1 gene; ESR1m, ESR1 mutated; 2l, second line; 3L, third line; mBC, metastatic breast cancer.

1. Internal market research.

ER+/HER2-, *ESR1*m mBC Patient Opportunity

ER+/HER2- represents the largest segment of mBC, and approximately 40% of that segment develops an *ESR1* mutation after endocrine therapy



As patients become more exposed to endocrine and CDK4/6 inhibitor therapy, ESR1m resistance develops

CT DNA testing is increasing the proportion of patients diagnosed and treated in 2L

The majority of ER+/HER2- patients with ESR1m are in the 2L and later setting due to exposure to endocrine and CDK4/6 therapy

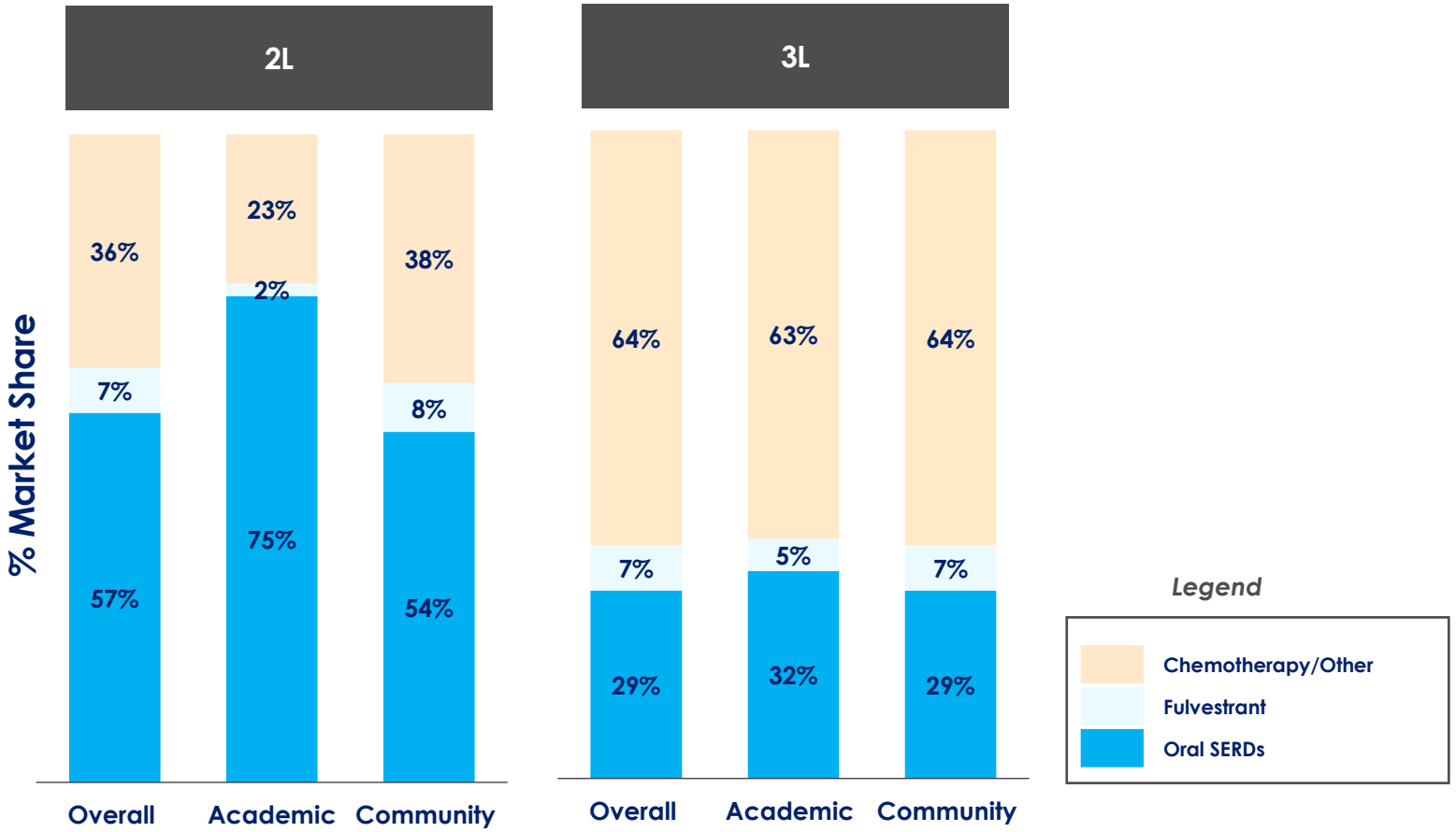
~20,000[1] patients with 2L/3L ER+/HER2-, *ESR1*m mBC represent potential $1B+ market in the U.S.

ER+/HER2-, estrogen receptor-positive, human epidermal growth factor receptor 2-negative; ESR1, estrogen receptor 1 gene; ESR1m, ESR1 mutation; mBC, metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; 2L, second line; 3L, third line.

1. Internal market research.

VEPPANU Will Enter a Dynamic Market Where Most Patients are Treated in the Community Setting

Current Therapies in 2L/3L ER+/HER2-, *ESR1*m mBC[1]



Market Opportunity

- Oral SERDs have been rapidly adopted, and are used in the majority of patients in 2L and ~30% of patients in 3L
- Chemotherapy and other therapies still represent more than 25% of patients in 2L and 60% patients in 3L
- Approximately 80% of patients are treated at community oncology practices, where nearly half of patients still do not receive oral SERDs in the 2L setting

2L, second line; 3L, third line; ER+/HER2-, estrogen receptor-positive, human epidermal growth factor receptor 2-negative; ESR1, estrogen receptor 1 gene; ESR1m, ESR1 mutated; MBC, metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; SERD, Selective Estrogen Receptor Degrader.

1. Internal Market Research Apr 2026

VEPPANU has the Potential to Become a Market-leading Treatment in 2L+ ER+/HER2-, *ESR1*m Metastatic Breast Cancer (mBC)

Proven Efficacy

- ***Significant Improvement in median Progression Free Survival (mPFS)***
  - ***Improved mPFS 2.4-fold, or 2.9 months*** (5.0 months vs. 2.1 months) vs. fulvestrant

Demonstrated Tolerability

- Manageable safety profile with ***low rates and severity of GI-related events***
- ***Low rates of treatment discontinuation (3%) and dose reductions (2%)***

Real-World Applicability

- Patient characteristics of those enrolled in VERITAC-2 were ***representative of real-world 2L+ setting, with 100% receiving prior CDK4/6i + ET***

Vepdegestrant demonstrated a median PFS of 5 months in *ESR1*-mutated patients and was well tolerated

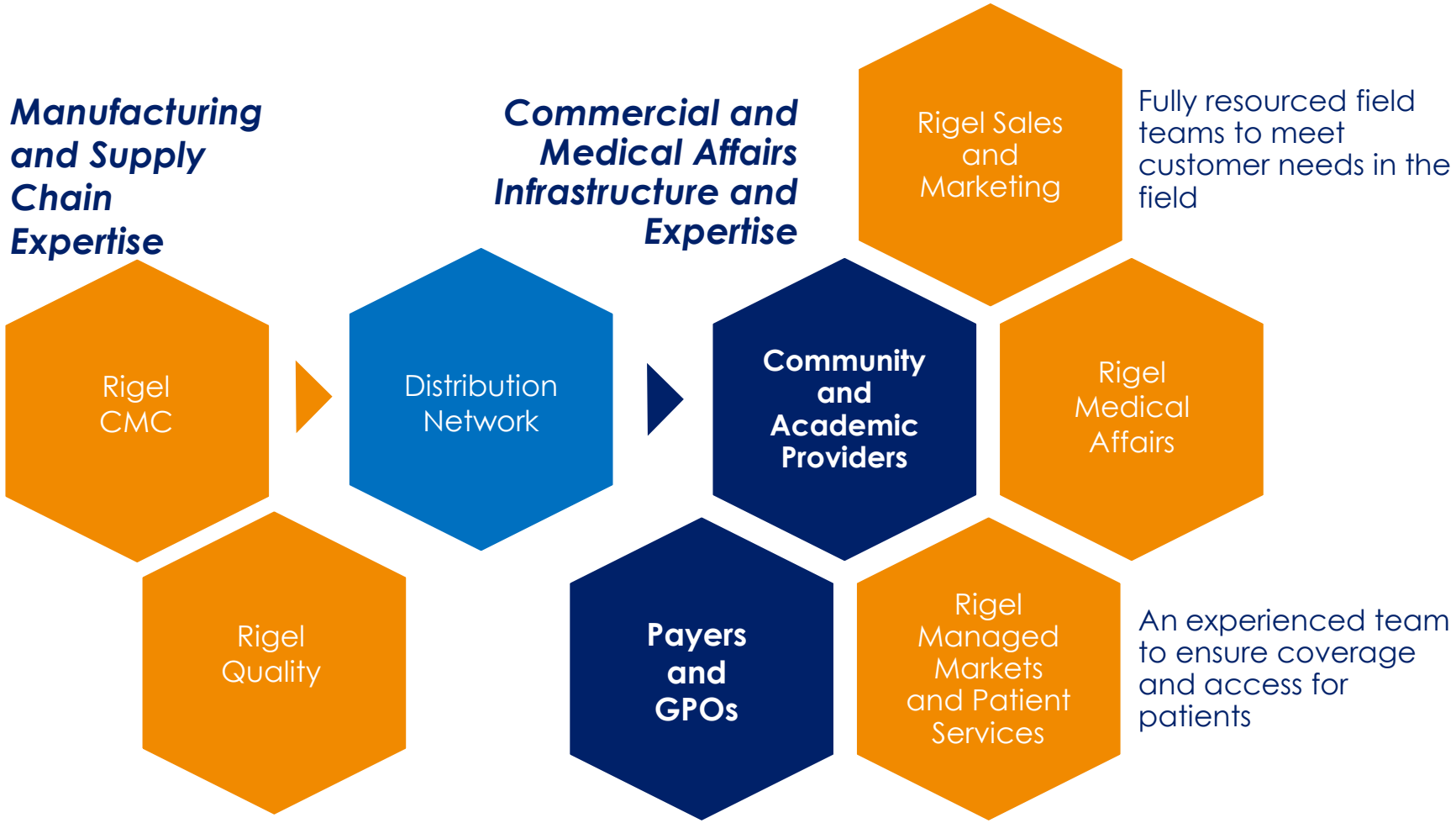
VERITAC-2 patient population is typical of the 2L/3L metastatic breast cancer patients that clinicians see[1]

2L+, second line-plus; ER+/HER2-, estrogen receptor-positive, human epidermal growth factor receptor 2-negative; *ESR1*, estrogen receptor 1 gene; *ESR1*m, *ESR1* mutated; GI, gastrointestinal; 2L, second line; 3L, third line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy.

1. Source: Hamilton. ASCO 2025. Abstr LBA1000. Campone. NEJM. 2025; 2025;393(6):556-568.

Rigel's Extensive Experience and Capabilities to Support Product Availability in August

Potential for VEPPANU to become Rigel's largest commercial product



One Rigel Team Preparing for Commercial Launch

- Successful track record of taking newly acquired assets to market quickly and efficiently
- Leveraging field and home office teams' capabilities to drive awareness and adoption
- Strong foundation that will be synergized to focus on rapidly growing VEPPANU
- Now engaging with healthcare providers

Advance Development Pipeline

Hematology and Oncology Focus Areas[1]

R289 IRAK1/4 Inhibitor

- Evaluating in a Phase 1b study for patients with R/R lower-risk MDS
  - Granted Fast Track and Orphan Drug designations by the FDA[2]
- Other potential indications under consideration

Olutasidenib m*IDH1* Inhibitor

- Strategic collaborations:
  - **MD Anderson**: Monotherapy or combination therapy in m*IDH1* AML, MDS, CCUS, CMML and MPN
  - **CONNECT**: Combination therapy in m*IDH1* high-grade glioma
  - **MyeloMATCH**: Combination therapy in m*IDH1* AML and MDS

IRAK1/4, interleukin receptor-associated kinases 1 and 4; R/R, relapsed/refractory; MDS, myelodysplastic syndrome; FDA, U.S. Food and Drug Administration; IDH1, isocitrate dehydrogenase-1; mIDH1, mutated IDH1; AML, acute myeloid leukemia; CCUS, clonal cytopenia of undetermined significance; CMML, chronic myelomonocytic leukemia; MPN, myeloproliferative neoplasm.

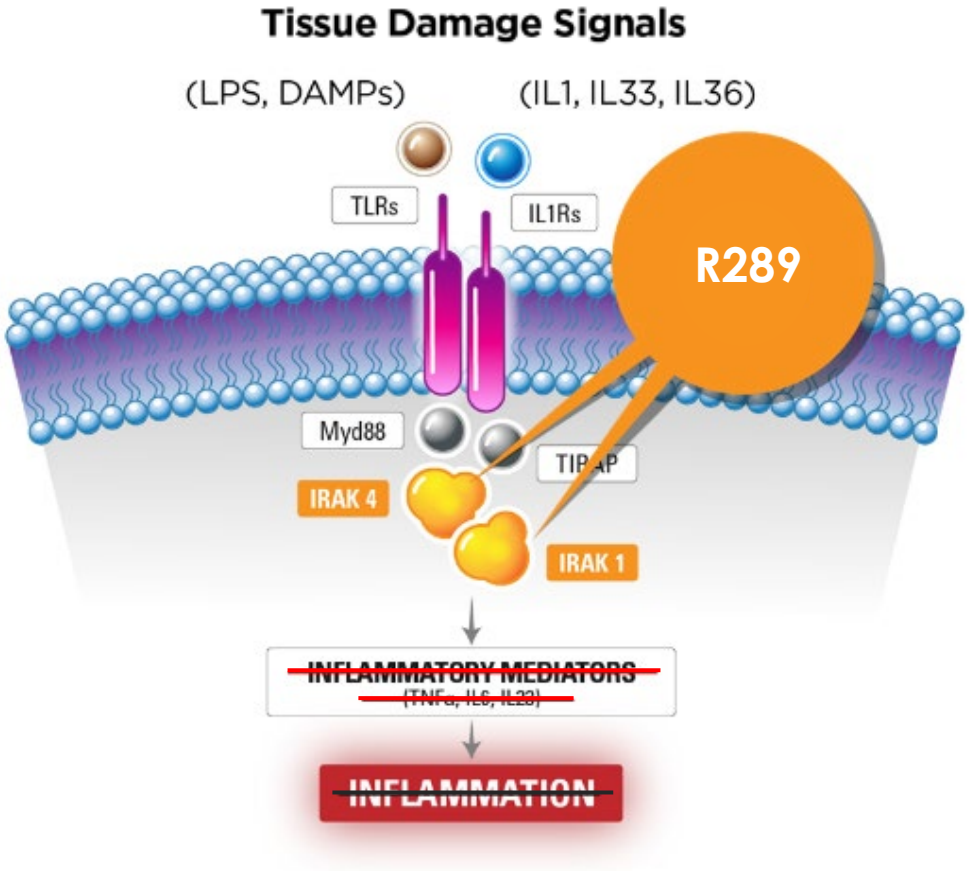
1. Investigational compounds in these indications and not approved by the FDA. **2**. R289 granted Fast Track designation for previously-treated transfusion dependent lower-risk MDS and Orphan Drug designation for MDS by the U.S. FDA.

R289
IRAK1/4 Inhibitor in Lower-Risk MDS

Targeting Inflammatory Pathways in Lower-Risk MDS

Dysregulation of immune/inflammatory signaling is associated with MDS

- IRAK1/4 are critical for downstream signaling of the IL-1R family and most TLRs, leading to a proinflammatory marrow environment and persistent cytopenias in patients with lower-risk MDS[1]
- Co-targeting IRAK1/4 may suppress inflammation and leukemic stem/progenitor cell function and restore hematopoiesis in MDS
- R835 is a selective dual inhibitor of IRAK1/4 that blocks TLR4 and IL-1R-dependent cytokine release *in vitro* and *in vivo*[2] and markedly suppressed LPS–induced cytokine release vs placebo in healthy volunteers (HV)[3]



Note: R289, an oral prodrug that is rapidly converted to R835 in the gut, is now being evaluated in a Phase 1b study in lower-risk MDS.

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

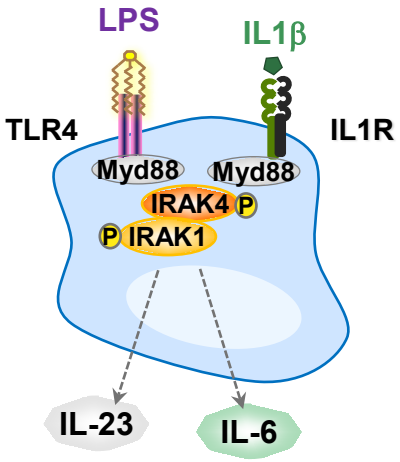
1. Sallman DA, et al. Front Oncol. 2016;6. **2.** Lamagna C et al. Ann Rheum Dis 2020;79 (suppl 1). **3.** Yan L et al. Ann Rheum Dis 2020;79 (suppl 1).

Targeting IRAK1 & IRAK4 Pathways in Inflammatory Disease

Dual inhibition of IRAK1 and IRAK4 provides stronger suppression of inflammatory cytokines compared to IRAK4-selective inhibitor alone in preclinical studies[1]

Kinase Assays

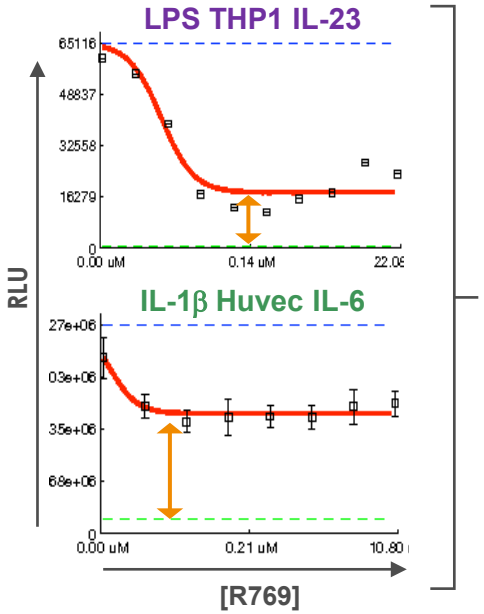
Cell-Based Assays



IRAK4-Selective Inhibitor

IRAK4 IC_{50} = 0.2nM

IRAK1 IC_{50} = Inactive



40-80%

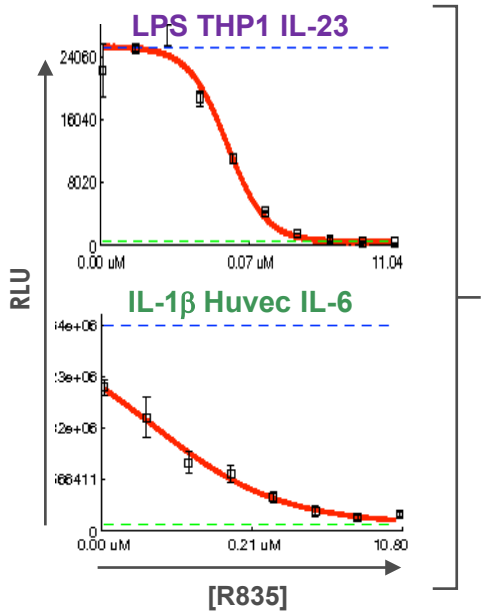
Inhibition of Cytokine Release

IRAK1/IRAK4 Dual Inhibitor

Rigel R835[2]

IRAK4 IC_{50} = 15nM

IRAK1 IC_{50} = 14nM



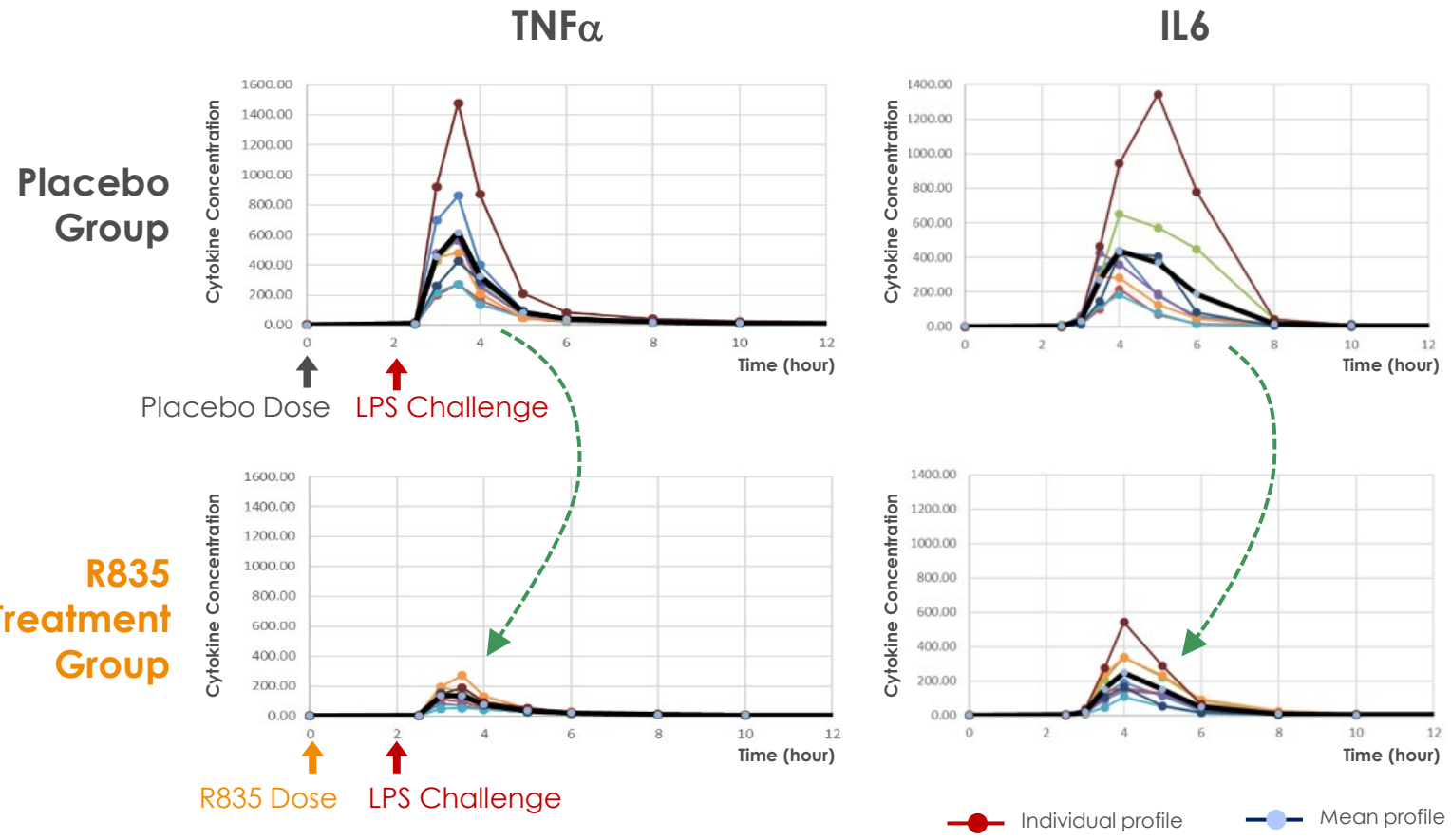
100%

Inhibition of Cytokine Release

IRAK1/4, interleukin receptor-associated kinases 1 and 4; TLR, toll-like receptor; IL, interleukin; LPS, lipopolysaccharide.
Note: No head-to-head clinical study has been conducted evaluating R835 against other agents included herein.
1. Rigel data on file. Lamagna C et al. Ann Rheum Dis 2020;79 (suppl 1). 2. R835 is an investigational compound not approved by the FDA.

R835[1] Proof-of-Mechanism in Healthy Volunteer Study[2]

Cytokine Response After LPS Challenge



First-In-Human study (n=82)

- R835 was well tolerated
- Linear PK profile and dose proportional exposure

Proof-of-Mechanism

- R835 markedly inhibited LPS-induced cytokine production vs placebo in HVs
- Inhibited TNFα, IL-6, and IL-8

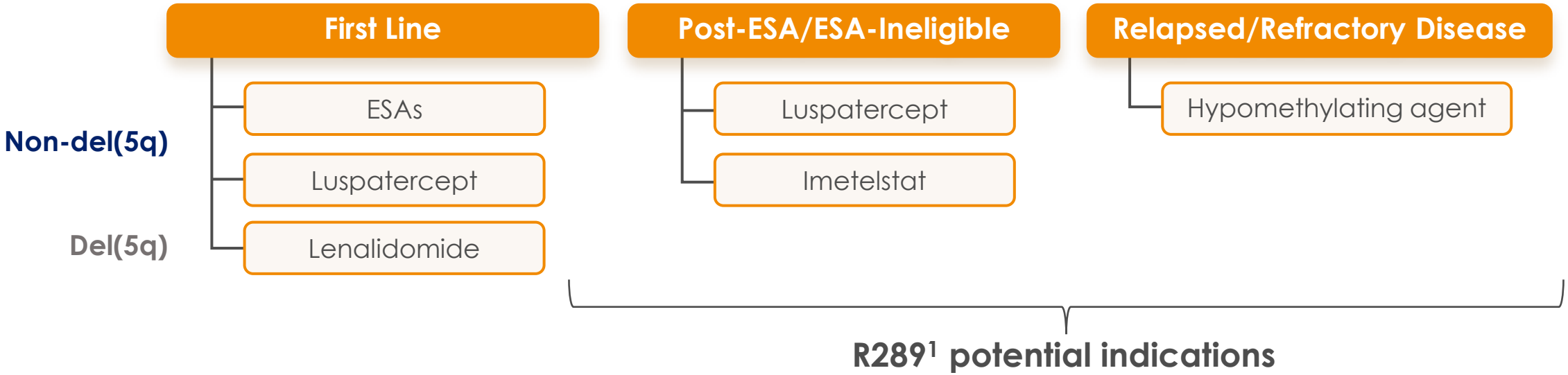
Note: R289, an oral prodrug that is rapidly converted to R835 in the gut, is now being evaluated in a Phase 1b study in lower-risk MDS.

LPS, lipopolysaccharides; TNFα, tumor necrosis factor-α; IL, interleukin; PK, pharmacokinetics; PD, pharmacodynamics.

1. R835 is an investigational compound not approved by the FDA. **2.** EULAR 2020 Poster Presentation -Abstract THU0219 - First-in-human Study of Safety, Pharmacokinetics and Pharmacodynamics of IRAK1/4 Inhibitor R835 in Healthy Subjects.

Lower-Risk MDS Treatment Landscape

- MDS is a clonal disorder of hematopoietic stem cells (HSCs) leading to dysplasia and ineffective hematopoiesis
  - Consequences: Cytopenias (anemia), infections, iron overload and organ dysfunction, progression to AML
- Primary goal of therapy: Reduce/limit transfusion-dependency
- Modest efficacy thus far with available therapies; there is room for improvement



New therapies needed for previously-treated TD LR-MDS patients that are R/R or ineligible for ESAs

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ESAs, erythropoiesis-stimulating agents; TD, transfusion dependent; LR-MDS, lower-risk myelodysplastic syndrome; R/R, relapsed or refractory.

1. Investigational compound not approved by the FDA.

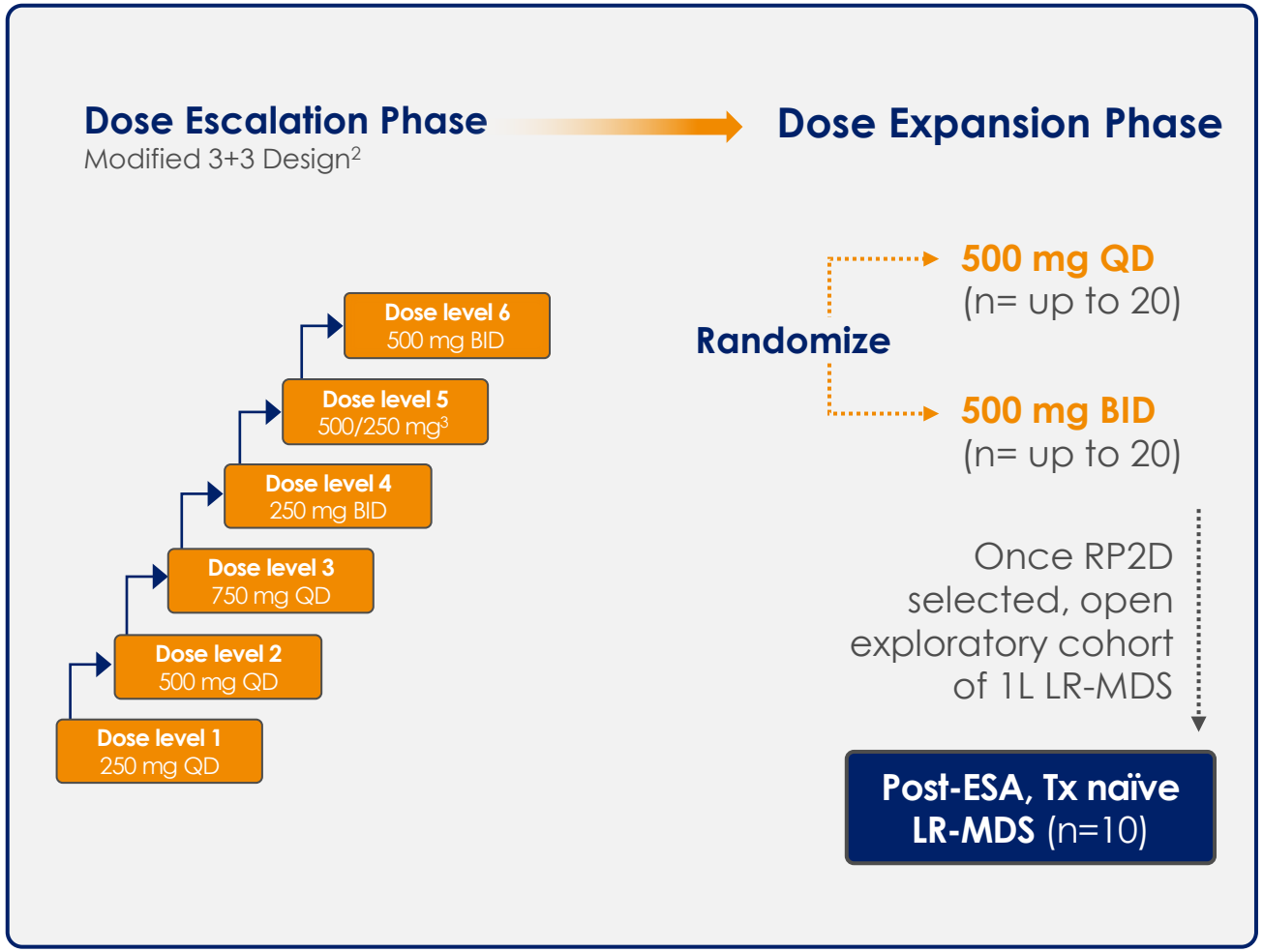
R289[1] Program Value Proposition for Lower-Risk MDS

Unmet Medical Need	• **~12,200 lower-risk MDS patients that have been previously treated[2]** • **Therapies for previously-treated transfusion dependent lower-risk MDS patients are lacking**
Novel Mechanism of Action	• **Dysregulated inflammatory signaling** is associated with MDS • **Co-targeting IRAK1/4 may** suppress inflammation and LSPC function and **restore hematopoiesis** • **Blocks TLR and IL-1R signaling** *in vitro*; **active in preclinical models of inflammation[3]**
Clinical Proof of Concept	• **Markedly suppressed LPS-induced cytokine release** was observed in a randomized controlled trial in healthy volunteers[4]
Regulatory Designations	• **Fast Track designation** for previously-treated transfusion dependent LR-MDS (Nov 2024) • **Orphan Drug designation** for treatment of myelodysplastic syndromes (Jan 2025)
Encouraging Clinical Profile	• **Promising preliminary safety and efficacy in a Phase 1b study** in elderly, heavily pre-treated patients with R/R LR-MDS (n=33) (presented at ASH 2025)[5]

MDS, myelodysplastic syndrome; LR-MDS, lower-risk myelodysplastic syndrome; ESAs, erythropoiesis-stimulating agents; LSPC, liver stem/progenitor cells; TLR, toll-like receptor; IL-1R, interleukin 1 receptor; LPS, lipopolysaccharide; R/R, relapsed or refractory. **1.** Investigational compound not approved by the FDA. **2.** Rigel data analysis on file. Patient population represents previously-treated patients. **3.** Sallman DA, et al. Front Oncol. 2016;6. **4.** Yan L et al. Ann Rheum Dis 2020;79 (suppl 1). **5.** Garcia-Manero et al. Blood (2025) 146 (Supplement 1): 489.

R289[1]: Phase 1b Study in Relapsed/Refractory Lower-Risk MDS

Open-label, multicenter study to evaluate the safety, tolerability, PK and preliminary efficacy of R289 in patients with LR-MDS (NCT05308264)



Key Eligibility Criteria

- R/R LR-MDS or inadequate response to prior therapies. Del(5q): R/R to lenalidomide
- Symptomatic anemia (Hb ≤9.0 g/dL) or TD (≥2u RBCs/16wks) in dose escalation; TD in dose expansion

Assessments

- Hematologic responses [TI and HI-E] per IWG 2018 criteria[4] and other responses per IWG 2006 criteria[5], from 8 weeks

Primary Endpoints

- Incidence of adverse events and dose-limiting toxicities

Secondary Endpoints

- Transfusion independence, hematologic improvement, response rates
- PK / PD
- Patient-reported outcomes (FACIT-Fatigue scale)

Updated data presented at ASH 2025

MDS, myelodysplastic syndrome; LR-MDS, lower-risk MDS; PK, pharmacokinetics; QD, daily; BID, twice daily; RP2D, recommended Phase 2 dose; Tx, treatment; Hb, hemoglobin; TD, transfusion dependent; TI, transfusion independence; HI-E, hematologic improvement - erythroid; PD, pharmacodynamics; FACIT-Fatigue scale, The Functional Assessment of Chronic Illness Therapy – Fatigue Scale.

1. Investigational compound not approved by the FDA. **2.** Jaki T et al. *Cancer Chemother Pharmacol.* 2013; 71. **3.** Split dose: 500 mg q AM, 250 mg q PM. **4.** Platzbecker U et al. Blood 2019;133(10). **5.** Cheson BD et al. Blood 2006;108.

Safety and Efficacy Results from a Phase 1b Study of R289 in Patients with Relapsed/Refractory Lower-Risk MDS

Patient Characteristics

Elderly, heavily pre-treated patient population with a high baseline transfusion burden

Data cutoff: October 28, 2025	All Patients (n=33)
Median age, years (range)	75 (50 - 84)
≥ 75 years	19 (58%)
Sex (M : F)	70% : 30%
IPSS-R Classification (Low: Intermediate: Ring sideroblast (RS)- : RS+)	67% : 33% : 67% (22) : 33% (11)
Median no. prior therapies	3 (1 - 8)
Prior hypomethylating agent (HMA)	22 (67%)
Prior luspatercept	25 (76%)
Prior erythropoiesis stimulating agent (ESA)	24 (73%)
Prior imetelstat	2 (6%)
High transfusion burden (HTB) (≥ 8u RBCs/prior 16 weeks)	20 (61%)
Low transfusion burden (LTB) (3-7u RBCs/prior 16 weeks)	11 (33%)
Non-transfused (NT)	2 (6%)
Mean baseline ANC (range), 10^9/L (range)	2.4 (0.3 - 5.4)
ANC <1.0 x 10^9/L	5 (15%)
Mean baseline platelet count (range)	183 (32 - 524)
Plts <100 x 10^9/L	7 (21%)

IPSS-R, International Prognostic Scoring System-Revised; RBCs, red blood cells; ANC, absolute neutrophil count; Plts, platelets.

Source: Garcia-Manero et al. Blood (2025) 146 (Supplement 1): 489.

Safety

R289 was generally well tolerated with a low incidence of Grade 3/4 cytopenias and infections

- All dose levels were generally well tolerated
- One DLT (G3 ALT/G4 AST increase) occurred at 750 mg QD
  - No evidence of dose-dependent toxicity across the other dose groups
- 3 patients (9%) discontinued treatment due to an AE (hyperuricemia, ALT/AST increase, fall/hip fracture)
- Serious adverse events (SAEs) occurred in 17 patients (52%). SAEs occurring in ≥2 patients: pneumonia (n=5), upper GI bleed (n=2); all were unrelated
- No study drug-related deaths occurred in the treatment period

TEAEs Occurring in at Least 18% (≥6) of Patients by Dose Level[1]

	Total (N = 33)		250 mg QD (N = 3)		500 mg QD (N = 6)		750 mg QD (N = 6)		250 mg BID (N = 6)		500/250 mg QD (N = 6)		500 mg BID (N = 6)	
Preferred Term	**Any n (%)**	**G3/4 n (%)**	Any n (%)	G3/4 n (%)	Any n (%)	G3/4 n (%)	Any n (%)	G3/4 n (%)	Any n (%)	G3/4 n (%)	Any n (%)	G3/4 n (%)	Any n (%)	G3/4 n (%)
Diarrhea	**10 (30)**	**0**	0	0	1 (17)	0	4 (67)	0	1 (17)	0	2 (33)	0	2 (33)	0
Constipation	**9 (27)**	**0**	0	0	1 (17)	0	2 (33)	0	0	0	4 (67)	0	2 (33)	0
Fatigue	**9 (27)**	**0**	2 (67)	0	4 (67)	0	2 (33)	0	1 (17)	0	0	0	0	0
ALT increased	**8 (24)**	**3 (9)**	0	0	0	0	3 (50)	2 (33)	1 (17)	0	3 (50)	1 (17)	1 (17)	0
AST increased	**8 (24)**	**3 (9)**	0	0	0	0	3 (50)	2 (33)	1 (17)	1 (17)	3 (50)	0	1 (17)	0
Creatinine increased	**7 (21)**	**0**	1 (33)	0	1 (17)	0	1 (17)	0	3 (50)	0	0	0	1 (17)	0
Cough	**7 (21)**	**0**	0	0	1 (17)	0	3 (50)	0	1 (17)	0	1 (17)	0	1 (17)	0
Anemia	**6 (18)**	**6 (18)**	0	0	3 (50)	3 (50)	1 (17)	1 (17)	2 (33)	2 (33)	0	0	0	0
Chills	**6 (18)**	**0**	0	0	0	0	1 (17)	0	3 (50)	0	1 (17)	0	1 (17)	0
Dyspnea	**6 (18)**	**0**	0	0	2 (33)	0	2 (33)	0	0	0	2 (33)	0	0	0
Nausea	**6 (18)**	**0**	0	0	1 (17)	0	3 (50)	0	1 (17)	0	1 (17)	0	0	0
Neutrophils decreased	**6 (18)**	**5 (15)**	0	0	0	0	4 (67)	3 (50)	0	0	1 (17)	1 (17)	1 (17)	1 (17)
Pneumonia	**6 (18)**	**5 (15)**	1 (33)	1 (33)	1 (17)	1 (17)	1 (17)	1 (17)	0	0	2 (33)	1 (17)	1 (17)	1 (17)

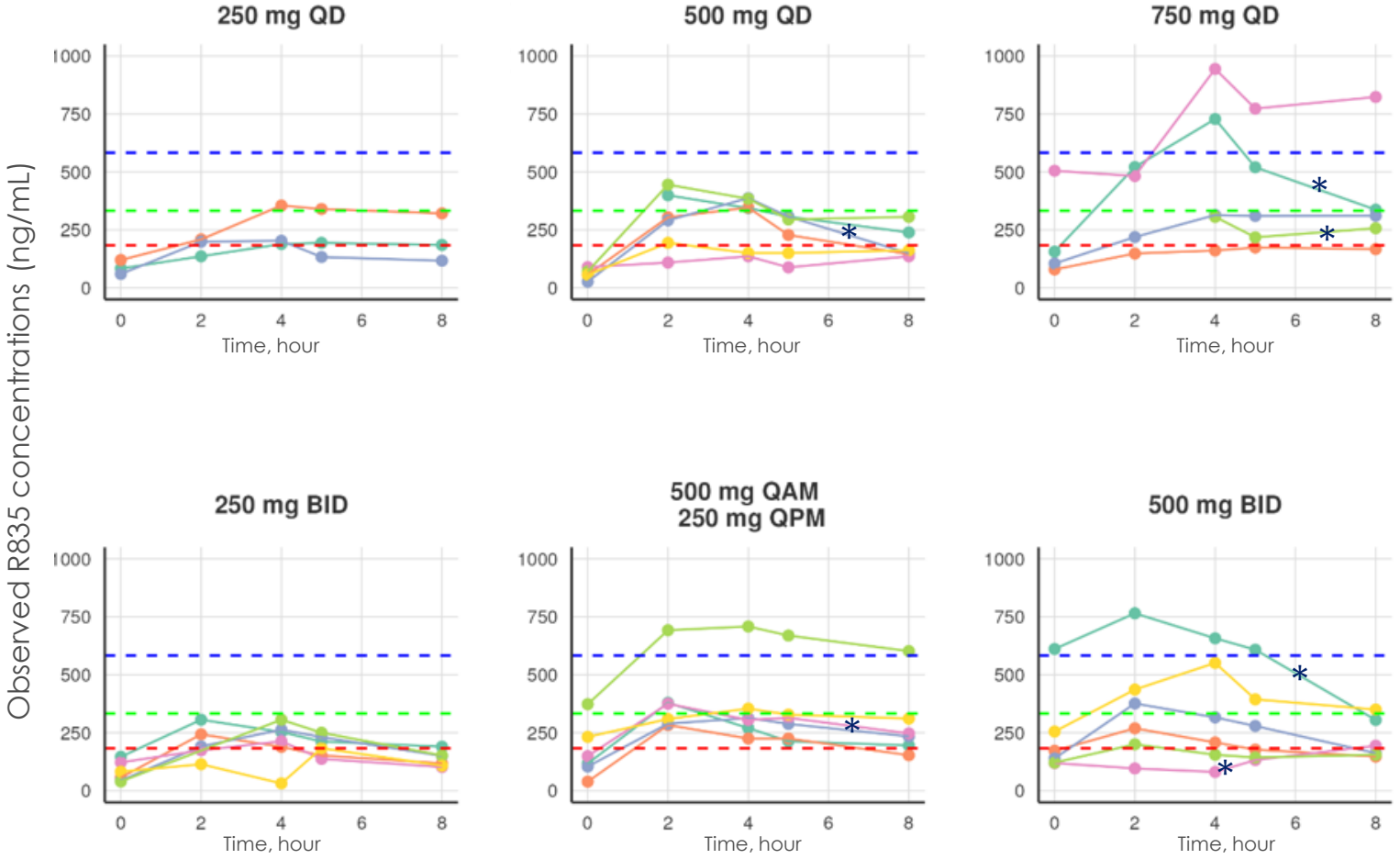
DLT, dose limiting toxicity; G, grade; ALT, alanine aminotransferase; AST, aspartate aminotransferase; QD, once daily; AE, adverse event; TEAE, treatment-emergent adverse event; BID, twice daily.

Source: Garcia-Manero et al. Blood (2025) 146 (Supplement 1): 489.

1. TEAEs include related and unrelated adverse events.

Pharmacokinetics

R835 plasma concentrations (administered as R289) by dose level (Cycle 2 Day 1[1])



- R835 exposure increased with increasing R289 dose
- At doses ≥500 mg once daily (QD), R835 steady state plasma concentrations reached or exceeded those resulting in 50-90% inhibition of LPS-induced cytokine release (---) previously observed in healthy volunteers[2]

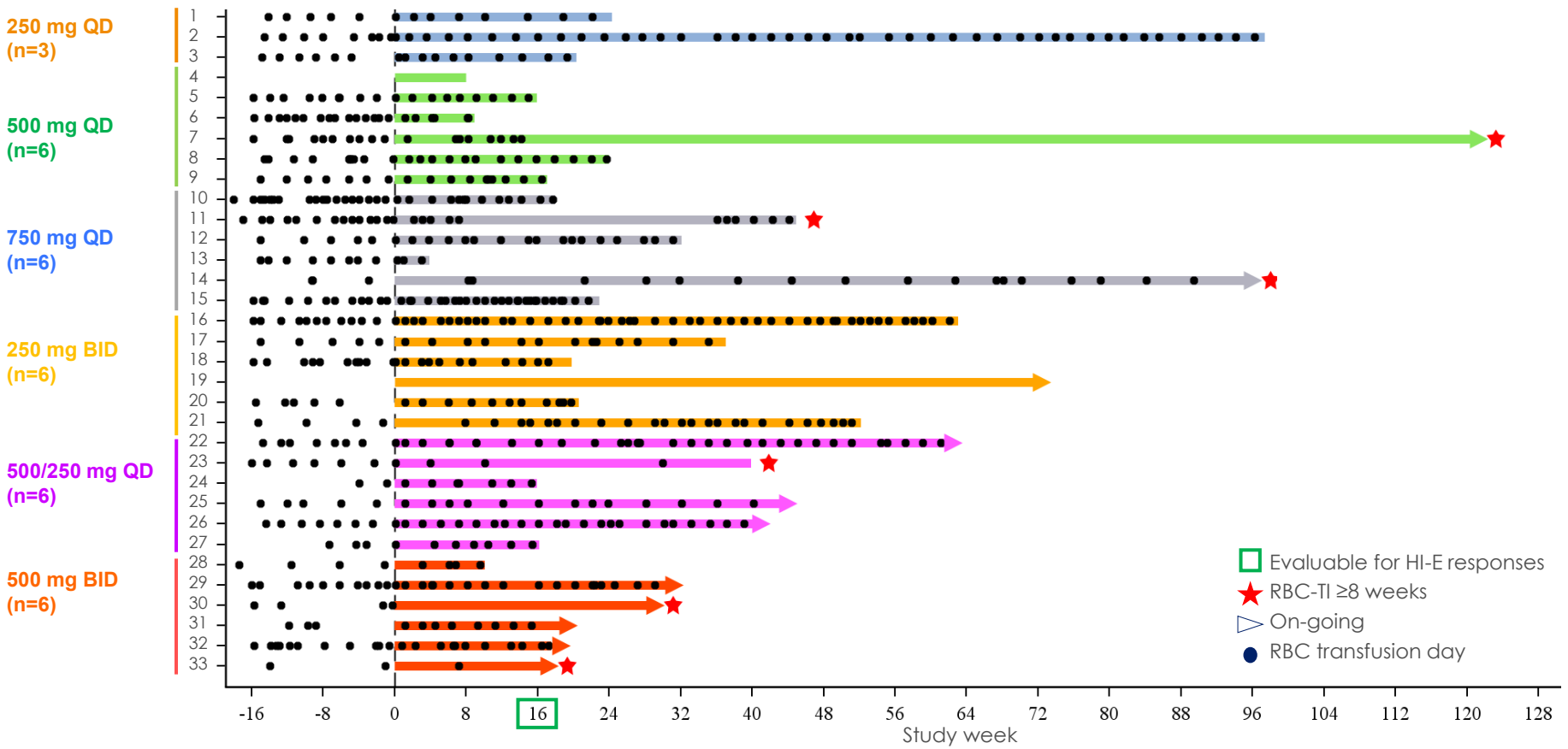
% inhibition of LPS-induced cytokine release in HV[2]
---- 90% inhibition
---- 50% inhibition
---- 25% inhibition

* Patients achieving RBC-TI

Note: R289 is an oral prodrug of R835. Star placement in table for identification purposes.
Dose limiting toxicity: G3 ALT/G4 AST ↑ in 1 pt at 750 mg QD (PK data not included in table).
QD, once daily; QAM, morning dose; QPM, evening dose; BID, twice daily; LPS, lipopolysaccharide; HV, healthy volunteers; RBC-TI, red blood cell transfusion independence.
Source: Garcia-Manero et al. Blood (2025) 146 (Supplement 1): 489.

1. Cycle 2 Day 1 is day 29. **2.** Yan L et al. Ann Rheum Dis 2020;79 (suppl 1).

RBC Transfusion Events by Dose Group



- Median duration of treatment: 5.5 months (range: 0.9 - 27.7 months)
- **6/18 (33%) evaluable TD patients receiving ≥500 mg QD achieved RBC-TI >8 weeks;** 4 >16 weeks; 3 >24 weeks
- **Median time to onset of RBC-TI:** 1.9 months
- **Median duration of RBC-TI:** 22.9 weeks (9 - 104.3)

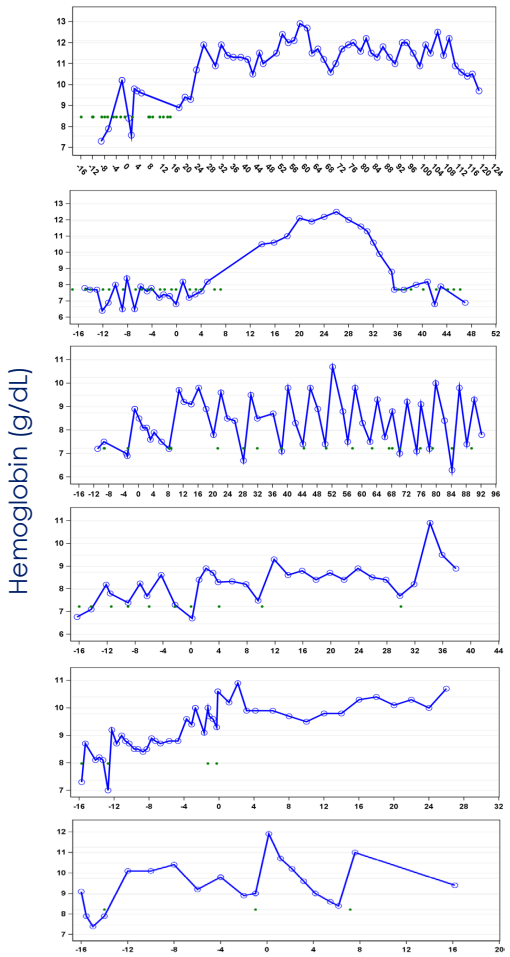
Note: Patients listed in order of enrollment.

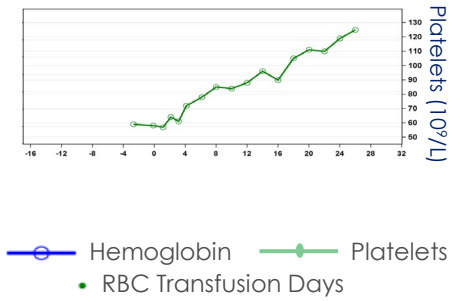
RBC, red blood cell; QD, once daily; BID, twice daily; HI-E, hematologic improvement-erythroid; TD, transfusion dependent; RBC-TI, red blood cell transfusion independence.

Source: Garcia-Manero et al. Blood (2025) 146 (Supplement 1): 489.

Summary of Patients Achieving RBC-TI

Peak hemoglobin increases ranging from 2.9 - 6.1 g/dL vs baseline occurred in patients achieving RBC-TI





Pt ID	Sex, Age	Dose Level	BL RBCs	Prior Therapies	Response Duration
7	76, M	500 mg QD	HTB	Darbopoetin, Canakinumab, ALK2 inhibitor, Decitabine	24.0 m→
11	59, M	750 mg QD	HTB	Azacitidine, Lenalidomide, Luspatercept	28.9 w
14	50, F	750 mg QD	LTB	Darbopoetin, Luspatercept	12.4 w
23	66, M	500/250 mg QD	LTB	Azacitidine, Luspatercept, Darbopoetin	19.7 w
30	79, M	500 mg BID	LTB	Canakinumab, Azacitidine	26.0 w→
33	72, F	500 mg BID	LTB	Azacitidine + rigosertib	9.0 w→

TI, transfusion independence; ID, identification; RBC, red blood cell; QD, once daily; HTB, high transfusion burden; LTB, low transfusion burden; ALK, anaplastic lymphoma kinase; w, weeks; m, months.

Source: Garcia-Manero et al. Blood (2025) 146 (Supplement 1): 489.

ASH 2025 Data Summary

R289 was Generally Well Tolerated

- Elderly, heavily pre-treated lower-risk MDS patient population, the majority of whom were high transfusion at baseline
  - The incidence of Grade 3/4 cytopenias and infections was low

Encouraging Preliminary Signs of Efficacy

- RBC-TI was achieved by 33% (6/18) of evaluable transfusion dependent patients receiving R289 doses ≥500 mg QD, with durable responses >24 weeks occurring in 3 patients thus far
  - Peak hemoglobin increases ranging from 2.9 - 6.1 g/dL vs. baseline occurred in patients achieving RBC-TI
  - 5/6 patients achieving RBC-TI had received prior HMAs

MDS, myelodysplastic syndrome; RBC-TI, red blood cell transfusion independence; QD, once daily; HMAs, hypomethylating agents; LPS, lipopolysaccharides.

Source: Garcia-Manero et al. Blood (2025) 146 (Supplement 1): 489.

R289 Development Next Steps

Lower-Risk MDS

- Complete enrollment of the dose expansion phase and selection of the recommended Phase 2 dose for future clinical studies (2H 2026)
  - Share updated top-line data from dose expansion phase by end of 2026
  - Open exploratory cohort of post-ESA, treatment naïve patients following selection of recommended Phase 2 dose
- Upon completion of Phase 1b study, follow-up with FDA about a potential registrational study

Other Potential Indications

- Evaluate R289 in other potential indications

MDS, myelodysplastic syndrome; ESA, erythropoiesis-stimulating agent; FDA, U.S. Food and Drug Administration.

Olutasidenib
mIDH1 Inhibitor

rigel

Strategic Alliance with MD Anderson Cancer Center to Advance Olutasidenib in AML and Other Cancers[1]

Five studies are open for enrollment

Rigel and The University of Texas MD Anderson Cancer Center are evaluating and supporting olutasidenib in combination with other agents to treat newly-diagnosed and relapsed/refractory patients with *IDH1*-mutated:

- AML
- Higher-risk MDS, CMML and advanced MPN

The collaboration is also supporting the evaluation of olutasidenib as:

- Monotherapy in *IDH1*-mutated CCUS & lower-risk MDS/CMML
- Post-transplant maintenance therapy for *IDH1*-mutated hematologic malignancies
- Combination with co-targeted therapy in patients with R/R *IDH1*-mutated myeloid malignancies harboring activated signaling pathway mutations

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CCUS, clonal cytopenia of undetermined significance; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms

1. Investigational compound in these indications and not approved by the FDA. Please see Important Safety Information on slides 60 & 61. Please visit www.REZLIDHIA.com for Full Prescribing Information, including Boxed WARNING.

rigel

Advancing Olutasidenib into m*IDH1* Glioma[1]

CONNECT's TarGeT Phase 2 Clinical Study

- Gliomas account for 29-35% of CNS tumors in children, adolescents & young adults[2]
- As part of CONNECT's "TarGeT" study in HGG, olutasidenib is being evaluated in combination with temozolomide as a maintenance regimen in newly-diagnosed adolescent and young adult patients (ages 12 to 39 years) with *IDH1* mutation positive HGG in the Rigel-sponsored "TarGeT-D" Phase 2 study arm
  - Study is open for enrollment

IDH1, isocitrate dehydrogenase-1; m*IDH1*, mutated IDH1; HGG, high-grade glioma.

1. Investigational compound in this indication and not approved by the FDA. **2.** Diwanji TP, et al. Adolesc Health Med Ther. 2017 Sep 22;8:99-113.

Potential to Evaluate Olutasidenib in First-Line AML and MDS in MyeloMATCH Precision Medicine Trial

NIH and NCI's MyeloMATCH is a group of precision medicine clinical trials for MDS and AML

- Patients will complete initial screening and will be assigned to a trial evaluating therapies that target their specific disease mutations

Planned study will evaluate olutasidenib in combination with other agents in patients with newly diagnosed m*IDH1* AML and MDS

NIH, National Institutes of Health; NCI, National Cancer Institute; MyeloMATCH, Myeloid Malignancies Molecular Analysis for Therapy Choice; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; IDH1, isocitrate dehydrogenase-1; mIDH1, mutated IDH1.

Maintain Financial Discipline

Q1 2026 Highlights

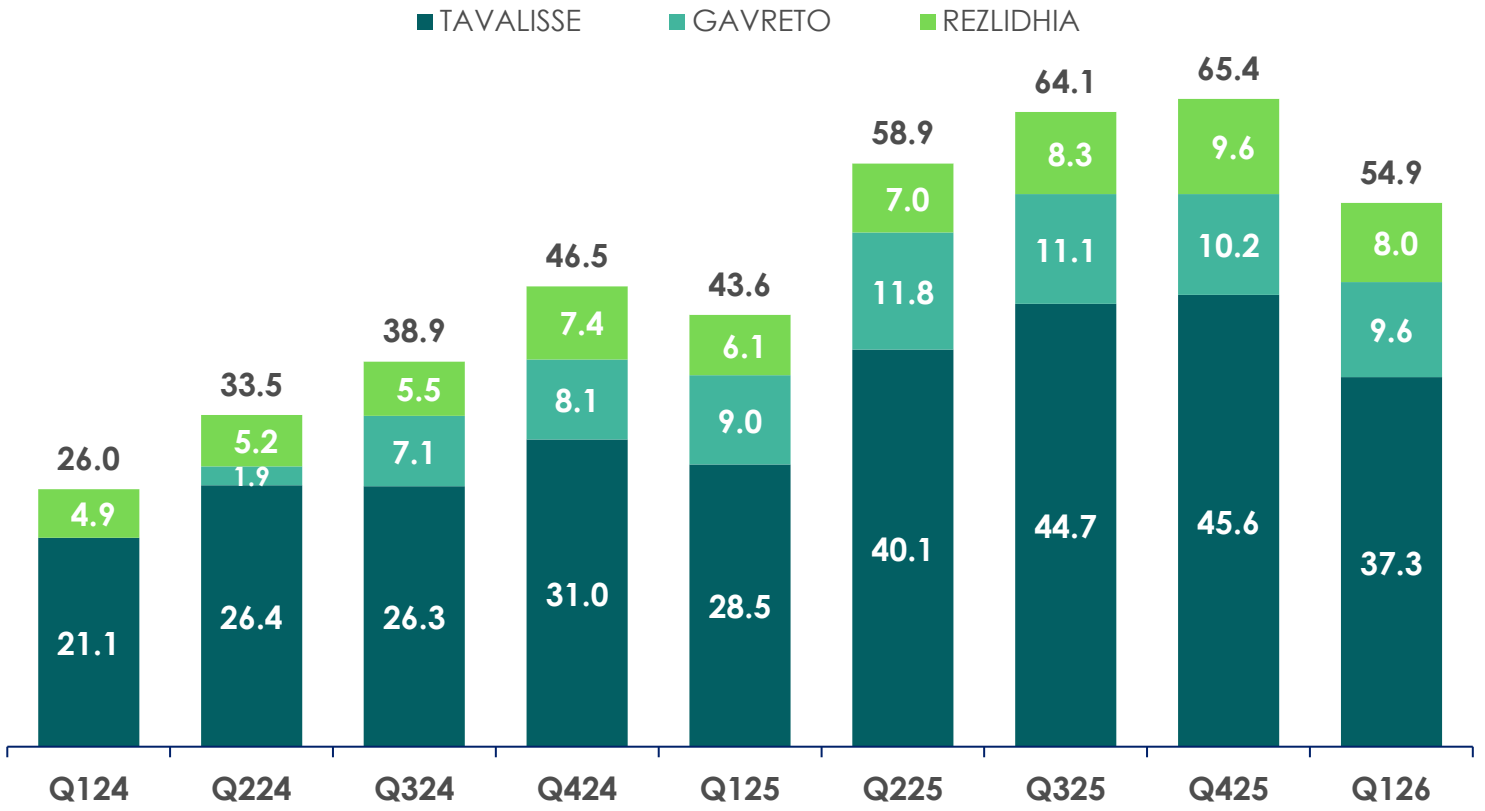
Q1 2026 Net Product Sales: $54.9M

- TAVALISSE $37.3M
- GAVRETO $9.6M
- REZLIDHIA $8.0M

Q1 2026 Contract Revenues: $3.9M

- Grifols $1.8M
- Kissei $1.8M
- Medison $0.3M

Net Product Sales ($M)



Q1 2026 Financial Overview

(in thousands)

	Three Months Ended March 31,	
	2026	2025
Revenues		
Net Product Sales	$ 54,923	$ 43,550
Contract revenues from collaborations	3,895	9,783
Total revenues	58,818	53,333
Costs and expenses:		
Cost of product sales	4,606	4,409
Research and development	11,676	8,436
Selling, general and administrative	30,651	27,715
Total costs and expenses	46,933	40,560
Income from operations	11,885	12,773
Interest income	1,205	591
Interest expense	(1,433)	(1,853)
Income before income tax	11,657	11,511
Provision for income tax	3,003	65
Net income	$ 8,654	$ 11,446

	As of	
	March 31, 2026	December 31, 2025
Cash, Cash Equivalents and Short-term Investments	$ 146,684	$ 154,955

2026 Financial Outlook[1]

- Total revenues of ~$275 to $290M
  - Net product sales of ~$255M to $265M
  - Contract revenues of ~$20M to $25M
- Anticipate will report positive net income for the full year 2026, while funding existing and new clinical development programs

In early May, Rigel restructured its credit relationship with MidCap Financial to replace its existing term loan credit facility with a revolving credit facility

In mid-April, Eli Lilly notified Rigel that it will terminate the collaboration agreement with Rigel[2]

1. Note: 2025 contract revenues from collaborations and total revenue included $40M in non-cash contract revenues related to Rigel's agreement with Eli Lilly (Q2 2025). **2.** The termination will become effective on June 15, 2026.

Exclusive Global License Agreement to Develop, Manufacture and Commercialize VEPPANU

Key Transaction Terms

Arvinas and Pfizer will receive:

- **$70M** upfront fee
- **$15M** upon the successful completion of certain transition activities
- Additional potential milestone payments: **$320M**
  - Regulatory Milestones: **$60M**
  - Commercial Milestones: **$260M**
- Tiered Royalties: Mid-teens to mid-twenties
- Pfizer and Arvinas remain responsible for current clinical trials
  - Rigel will contribute up to $40 million over the next 4 years

2026 Updates and Key Priorities

Grow Commercial Business

- **Commercially launch VEPPANU in August**
- **Q1 2026 total revenues of $58.8M**
  - Net product sales of $54.9M
  - Contract revenues from collaborations of $3.9M

In-Licensing / Business Development

- **In-license of VEPPANU™ (vepdegestrant), an oral PROTAC with the potential to be an important new treatment option for patients with 2L+ ER+/HER2-, *ESR1*m advanced or metastatic breast cancer**

Maintain Financial Discipline

- **Leverage existing commercial and operating infrastructure during integration of vepdegestrant to drive financial synergies**
- **2026 Outlook:[1] Total revenues: ~$275M to $290M**
  - Net product sales of ~$255M to $265M
  - Contract revenues of ~$20M to $25M

Advance Development Pipeline

- **R289 Phase 1b study in lower-risk MDS:**
  - Complete dose expansion and select RP2D for future clinical studies (2H 2026)
  - Share updated top-line data by end of 2026
  - Upon completion of the Phase 1b study, follow-up with FDA about a potential registrational study

PROTAC, PROteolysis TArgeting Chimera; 2L+, second line-plus; ER+/HER2-, estrogen receptor-positive, human epidermal growth factor receptor 2-negative; ESR1, estrogen receptor 1 gene; ESR1m, ESR1 mutated; MDS, myelodysplastic syndrome; RP2D, recommended Phase 2 dose; FDA, U.S. Food and Drug Administration.

1. 2026 outlook as of May 5, 2026 and does not include vepdegestrant in-licensing transaction.

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 https://www.tavalisse.com/ for full Prescribing Information

To report side effects of prescription drugs to the FDA, visit https://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.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see https://www.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

WARNING: SERIOUS INFECTIONS, INCLUDING OPPORTUNISTIC INFECTIONS

GAVRETO may increase the risk for serious infections, including bacterial, fungal, viral and opportunistic infections, which can lead to hospitalization or death. Withhold, reduce the dose or permanently discontinue GAVRETO based on severity.

WARNINGS AND PRECAUTIONS

- **Serious Infections, including Opportunistic Infections:** GAVRETO may increase the risk for serious infections, including fatal and opportunistic infections. In the AcceleRET-Lung trial, infections occurred in 72% of patients who received GAVRETO, including 18% with Grade 3 and 3.7% with Grade 4 and 7% with fatal outcomes. Among the patients who received chemotherapy/immunotherapy, infections occurred in 52%, including 10% with Grade 3. Infections in the GAVRETO arm included pneumonia, urinary tract infection, opportunistic infections (such as pneumocystis jirovecii pneumonia, and fungal infections) and others. Monitor patients for signs and symptoms of infection and treat appropriately. Withhold, reduce the dose, or permanently discontinue GAVRETO based on severity.
- **Interstitial Lung Disease (ILD)/Pneumonitis:** Severe, life-threatening, and fatal interstitial lung disease (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 which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.
- **Hypertension:** 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 AST occurred in 49% of patients, including Grade 3 or 4 in 7% and increased 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 for 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.

IMPORTANT SAFETY INFORMATION (Cont.)

- **Hemorrhagic Events:** Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic 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:** Cases of tumor lysis syndrome (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.
- **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. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily. 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.

ADVERSE REACTIONS

- **The most common adverse reactions (≥ 25%)** were musculoskeletal pain, constipation, hypertension, diarrhea, fatigue, edema, pyrexia and cough. **The most 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.

DRUG INTERACTIONS

- **Strong or moderate CYP3A inhibitors and/or P-gp inhibitors:** Concomitant use with a strong or moderate CYP3A inhibitor and/or a P-gp inhibitor increases pralsetinib exposure, which may increase the risk of adverse reactions related to GAVRETO. Avoid coadministration of GAVRETO with a strong or moderate CYP3A and/or P-gp inhibitor. If coadministration with any of the above inhibitors cannot be avoided, reduce the GAVRETO dose.
- **Strong or moderate CYP3A inducers:** Concomitant use with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of GAVRETO. Avoid concomitant use of GAVRETO with strong or moderate CYP3A inducers. If coadministration of GAVRETO with strong or moderate CYP3A inducers cannot be avoided, increase the GAVRETO dose.

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise not to breastfeed during treatment with GAVRETO and for 1 week after the last dose.
- **Pediatric Use:** The safety and effectiveness of GAVRETO have not been established in pediatric patients with RET fusion-positive NSCLC or in pediatric patients younger than 12 years old with RET fusion positive thyroid cancer.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see https://www.GAVRETO.com/ for full Prescribing Information, including Boxed WARNING.

About VEPPANU™ (vepdegestrant)

INDICATION
VEPPANU is indicated for the treatment of adults with estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative, estrogen receptor–1 (ESR1)–mutated advanced or metastatic breast cancer, as detected by an FDA-authorized test, with disease progression following at least one line of endocrine therapy.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
QTc Interval Prolongation
VEPPANU can cause QT (QTc) interval prolongation. Correct electrolyte abnormalities, including hypokalemia and hypomagnesemia, prior to and during treatment with VEPPANU. Perform an ECG prior to initiation of treatment with VEPPANU and do not initiate VEPPANU in patients with QTc >470 msec. Repeat ECG approximately 4 weeks after initiating treatment and as clinically indicated. Avoid concomitant use of VEPPANU with strong CYP3A inhibitors or drugs known to prolong the QTc interval.

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

ADVERSE REACTIONS
Serious adverse reactions occurred in 9% of patients who received VEPPANU. The serious adverse reactions included any fracture (1.3%), fall, hypercalcemia, hepatic injury, pneumonia, musculoskeletal pain (0.6% each), and QTc prolonged (0.3%). Fatal adverse reactions occurred in 1.0% of patients who received VEPPANU, including dyspnea, cerebral ischemia, and unknown cause (one patient each).

Permanent discontinuation of VEPPANU due to an adverse reaction occurred in 2.9% of patients, dosage interruptions of VEPPANU due to an adverse reaction occurred in 14% of patients, and dosage reductions of VEPPANU due to an adverse reaction occurred in 1.9% of patients.

The most common (≥10%) adverse reactions, including laboratory abnormalities, were decreased white blood cells, increased AST, musculoskeletal pain, fatigue, decreased hemoglobin, decreased neutrophils, increased ALT, increased alkaline phosphatase, nausea, decreased blood potassium, increased bilirubin, decreased appetite, electrocardiogram QT prolonged, decreased platelets, and constipation.

Clinically relevant adverse reactions in <10% of patients who received VEPPANU included headache, hot flush, diarrhea, vomiting, bradycardia, and urinary tract infection.

DRUG INTERACTIONS
- **Strong CYP3A Inhibitors:** Avoid concomitant use of VEPPANU with strong CYP3A inhibitors. If concomitant use cannot be avoided, reduce VEPPANU dosage.
- **Strong CYP3A Inducers:** Avoid concomitant use with strong CYP3A inducers in patients receiving VEPPANU. If concomitant use cannot be avoided, increase VEPPANU dosage.
- **Certain P-gp Substrates:** Avoid concomitant use with certain P-gp substrates where minimal increases in concentration may lead to serious adverse reactions.
- **Certain UGT1A9 Substrates:** Refer to the Prescribing Information for UGT1A9 substrates where minimal increases in the concentration may lead to serious adverse reactions.

Avoid concomitant use of VEPPANU with other drugs with a known potential to prolong the QTc interval.

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

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

Please see https://www.VEPPANU.com/ for full Prescribing Information.

Thank You

www.rigel.com