Karyopharm® Therapeutics

BELIEVERS IN THE EXTRAORDINARY

Second Quarter 2025 Financial Results & Business Update

August 11, 2025

On Today's Call

- **Welcome**
  Brendan Strong, *SVP, Investor Relations and Corporate Communications*
- **Overview**
  Richard Paulson, *President and Chief Executive Officer*
- **Pipeline Update**
  Dr. Reshma Rangwala*, Chief Medical Officer and Head of Research*
- **Commercial Highlights**
  Sohanya Cheng, *Chief Commercial Officer and Head of Business Development*
- **Financial Results and Guidance**
  Lori Macomber, *Chief Financial Officer and Treasurer*
- **Closing Remarks**
  Richard Paulson, *President and Chief Executive Officer*
- **Q&A Session**

Forward-looking Statements and Other Important Information

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Karyopharm's guidance on its 2025 total revenue, 2025 U.S. net product revenue and 2025 R&D and SG&A expenses; Karyopharm's expected cash runway and liquidity; Karyopharm's exploration of strategic alternatives and financing transactions; beliefs about the market opportunity and annual peak revenue opportunities for selinexor; expectations with respect to commercialization efforts; the ability of selinexor to treat patients with multiple myeloma, endometrial cancer, myelofibrosis, diffuse large B-cell lymphoma and other diseases; and expectations with respect to the clinical development plans and potential regulatory submissions of selinexor. Such statements are subject to numerous important factors, risks and uncertainties, many of which are beyond Karyopharm's control, that may cause actual events or results to differ materially from Karyopharm's current expectations. For example, there can be no guarantee that Karyopharm will successfully commercialize XPOVIO or that any of Karyopharm's drug candidates, including selinexor, will successfully complete necessary clinical development phases or that development of any of Karyopharm's drug candidates will continue. Further, there can be no guarantee that any positive developments in the development or commercialization of Karyopharm's drug candidate portfolio will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other factors, including the following: the adoption of XPOVIO in the commercial marketplace, the timing and costs involved in commercializing XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; the ability to obtain and retain regulatory approval of XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; Karyopharm's results of clinical and preclinical trials, including subsequent analysis of existing data and new data received from ongoing and future trials; the content and timing of decisions made by the U.S. Food and Drug Administration and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, including with respect to the need for additional clinical trials; the ability of Karyopharm or its third party collaborators or successors in interest to fully perform their respective obligations under the applicable agreement and the potential future financial implications of such agreement; Karyopharm's ability to enroll patients in its clinical trials; unplanned cash requirements and expenditures; substantial doubt exists regarding Karyopharm's ability to continue as a going concern; development or regulatory approval of drug candidates by Karyopharm's competitors for products or product candidates in which Karyopharm is currently commercializing or developing; the direct or indirect impact of the COVID-19 pandemic or any future pandemic on Karyopharm's business, results of operations and financial condition; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any of its products or product candidates. These and other risks are described under the caption "Risk Factors" in Karyopharm's Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, which was filed with the Securities and Exchange Commission (SEC) on May 12, 2025, and in other filings that Karyopharm may make with the SEC in the future. Any forward-looking statements contained in this presentation speak only as of the date hereof, and, except as required by law, Karyopharm expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. Karyopharm regularly uses its website to post information regarding its business, drug development programs and governance. Karyopharm encourages investors to use www.karyopharm.com, particularly the information in the section entitled "Investors," as a source of information about Karyopharm. References to www.karyopharm.com in this presentation are not intended to, nor shall they be deemed to, incorporate information on www.karyopharm.com into this presentation by reference. Other than the currently approved indications of XPOVIO, selinexor is an investigational drug that has not been approved by the FDA or any other regulatory agency, and the safety and efficacy of this drugs has not been established by any agency.

OVERVIEW

Richard Paulson
President and Chief Executive Officer

Focused on Transformative Myelofibrosis Opportunity

Exploring financing transactions and strategic alternatives to extend cash runway and maximize value

XPOVIO® (selinexor) Has a **Novel & Differentiated MoA** that has the Potential to Treat Various Cancers[1]

Growing Global Demand for XPOVIO/NEXPOVIO® (selinexor); Now Approved in 50 Countries

Myelofibrosis Peak Annual Revenue Opportunity of up to **~$1 Billion**[2,3,4]

Profitable, Commercial Organization in U.S. Can Be Leveraged Across Other Indications

Top-Line Data Expected in March 2026 from Phase 3 SENTRY Trial of Selinexor in Myelofibrosis

Continue to Invest in Focused Pipeline, including in Endometrial Cancer and Multiple Myeloma

1. Makker ASCO 2024; Tantravahi ASH 2023; Mechanism of Action (MoA). 2. Includes projected potential selinexor revenues in JAKi-naïve myelofibrosis. 3. Annual U.S. peak revenue opportunity is not guidance, but instead represents what the Company believes to be Karyopharm's peak revenue opportunity, if approved, based on internal estimates, including market research. 4. Pending positive data from the Phase 3 SENTRY trial and regulatory approval.

Efficient Development Spanning Seven Years, Consistently Building a Strong Profile for Potential Success in Myelofibrosis

Delivering for Myelofibrosis Patients

- Preclinical activity in myelofibrosis
- Demonstrated monotherapy activity signal (ESSENTIAL IST at ASH 2021)
- Initiated Phase 1 study in JAKi Naïve MF in combination with ruxolitinib
- Demonstrated potential strong combination activity signal in JAKi naïve patients (Phase 1 data at ASH 2022 and ASH 2023)
- Received Fast Track Designation and Orphan Drug Designation
- Initiated Phase 3 SENTRY trial of selinexor plus ruxolitinib
- Learned from other MF programs; aligned with FDA on updated primary endpoints, increasing PoS
- Phase 2 in JAKi pre-treated patients further demonstrates evidence of monotherapy activity, disease modification and improved tolerability
- Blinded safety data from Phase 3 may suggest improved safety profile based on extrapolated analysis; minimal TEAEs leading to discontinuation

Investigator Sponsored Trial (IST); Myelofibrosis (MF); Probability of Success (PoS)

Leading KOL Emphasizes the Unmet Need in Myelofibrosis and is a Strong Believer in Selinexor's Potential to Improve Outcomes for Patients

"I'm excited about the SENTRY trial because it is trying to move the myelofibrosis field forward by introducing combinations of therapy early on that don't have overlapping mechanisms of action, to try to get the deepest response possible to control the disease and hopefully have that durability that benefits the patient long term."

Dr. John Mascarenhas, Mount Sinai and Principal Investigator of Phase 3 SENTRY Trial

Myelofibrosis Represents a Transformative Opportunity, Building on our Foundation in Multiple Myeloma

~$113 million

(XPOVIO Net Product Revenue in 2024)

- ✓ Profitable commercial organization executing well in the highly competitive multiple myeloma marketplace
- ✓ Working to drive continued revenue growth in multiple myeloma

Up to ~$1 billion

(Myelofibrosis Peak U.S. Revenue Opportunity[1,2,3])

- ✓ 2024 ruxolitinib myelofibrosis U.S. sales of $1.1 billion[4]
- ✓ Complimentary to ruxolitinib, growing market from 30-35% responders to approximately 70% looking at spleen volume reduction of 35% or more (SVR35) and addressing key hallmarks of disease with upfront therapy
- ✓ 75% of U.S. physicians surveyed indicated intent to adopt combination therapy[5]
- ✓ Existing sales team already covers ~80% of community-based myelofibrosis accounts[6]

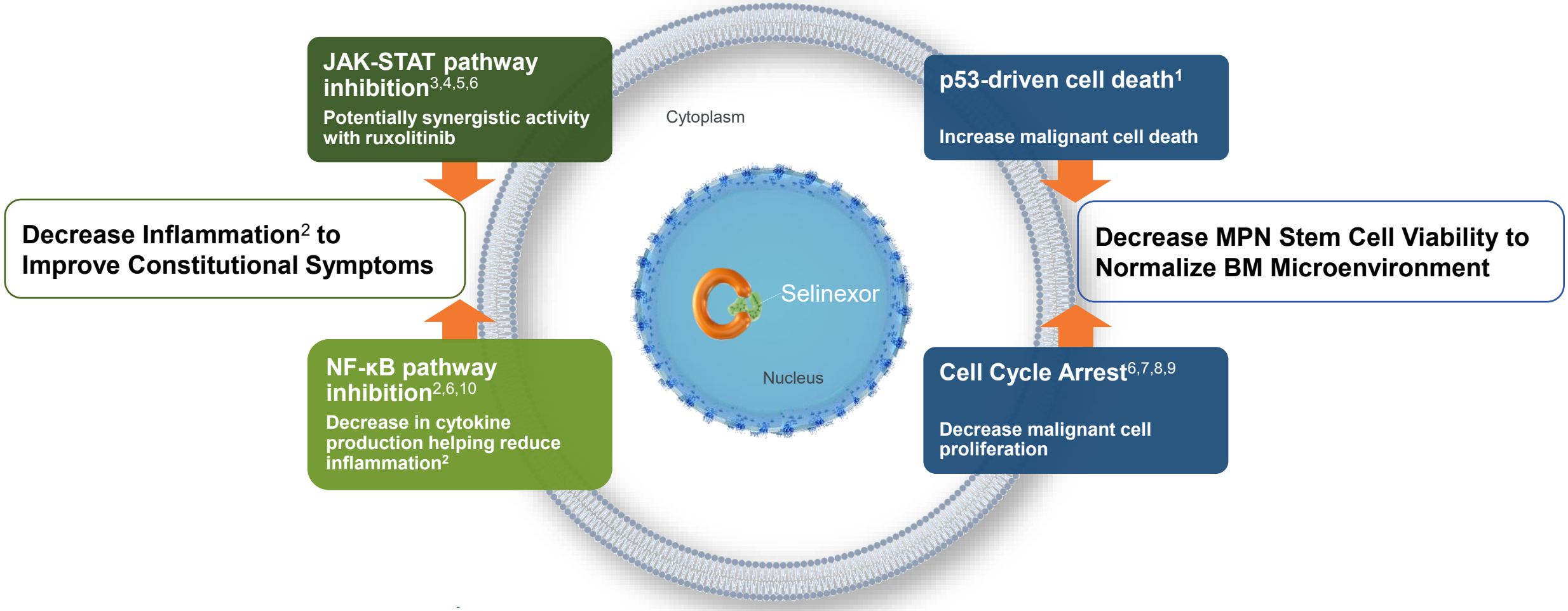
1. Includes projected potential selinexor revenues in JAKi-naïve myelofibrosis. 2. Annual U.S. peak revenue opportunity is not guidance, but instead represents what the Company believes to be Karyopharm's peak revenue opportunity, if approved, based on internal estimates, including market research. 3. Pending positive data from the Phase 3 SENTRY trial and regulatory approval. 4. Incyte Corporate website events and quarterly presentations. 5. Data on file; qualitative market research May 2023, N =25 MF treaters US hematology oncologists and medical oncologists. 6. Internal claims data analysis of multiple myeloma (MM) and myelofibrosis (MF) target list.

PIPELINE UPDATE

Reshma Rangwala, MD, PhD
Chief Medical Officer and Head of Research

XPO1 Inhibition is Potentially a Fundamental Mechanism in the Treatment of Myelofibrosis that Targets Both JAK-STAT and non-JAK-STAT Pathways[1-10]

Representing Opportunity for Additive or Synergistic Activity When Dosed in Combination with Ruxolitinib and Other JAK inhibitors, Plus Potential Use as Monotherapy



1. Yan D et al. Clin Cancer Res. 2019;25(7):2323-2335. 2. Kashyap T et al. Oncotarget. 2016;7(48):78883-78895. 3. Walker CJ et al. Blood. 2013;122(17):3034-3044. 4. Cheng Y et al. Mol Cancer Ther. 2014;13(3): 675-686. 5. Argueta C et al. Oncotarget. 2018;9(39);25529-25544. 6. Gandhi UH et al. Clin Lymphoma Myeloma Leukemia. 2018;18(5):335-345. 7. Gravina GL et al. BMC Cancer. 2015;15:941. 8. Garg M et al. Oncotarget. 2017;8(5):7521-7532. 9. Tan M et al. Am J Physiol Renal Physiol. 2014;307(11): F1179-1186. 10. Turner JG et al. Oncotarget. 2016;7(48):78896-78909.

Selinexor plus Ruxolitinib May Potentially Establish a New Paradigm by Substantially Improving Clinical Benefit for Myelofibrosis Patients*

Selinexor Plus Ruxolitinib

Four Key Pillars in Myelofibrosis

Spleen Volume Reduction

79% achieved SVR35 (ITT) at week 24[1]

Over 2X the responders compared to ruxolitinib historical spleen response at week 24[2]

100% efficacy evaluable patients achieved an SVR35 at anytime[1]

Symptom Improvement

Average **18.5 point improvement in absolute-TSS (abs-TSS)**[3] in the efficacy evaluable population at week 24

Fatigue excluded from **Abs-TSS** analysis

Hemoglobin Stabilization[4] and Decreased Transfusion Burden[5]

Lower rates of Grade 3+ anemia compared to physician's choice (PC) (primarily JAK inhibitors, including ruxolitinib)[5]

Similar rates of all-grade thrombocytopenia compared to PC[5]

Disease Modification

Substantial reduction in mutational burden, bone marrow fibrosis and key pro-inflammatory cytokines critical to myelofibrosis pathogenesis and symptom development[4,6]

Safety

Improving Safety Profile with Selinexor

Utilize lower dose of 60 mg with dual anti-emetics to potentially minimize AEs

Minimal discontinuations due to TEAEs[1,5]

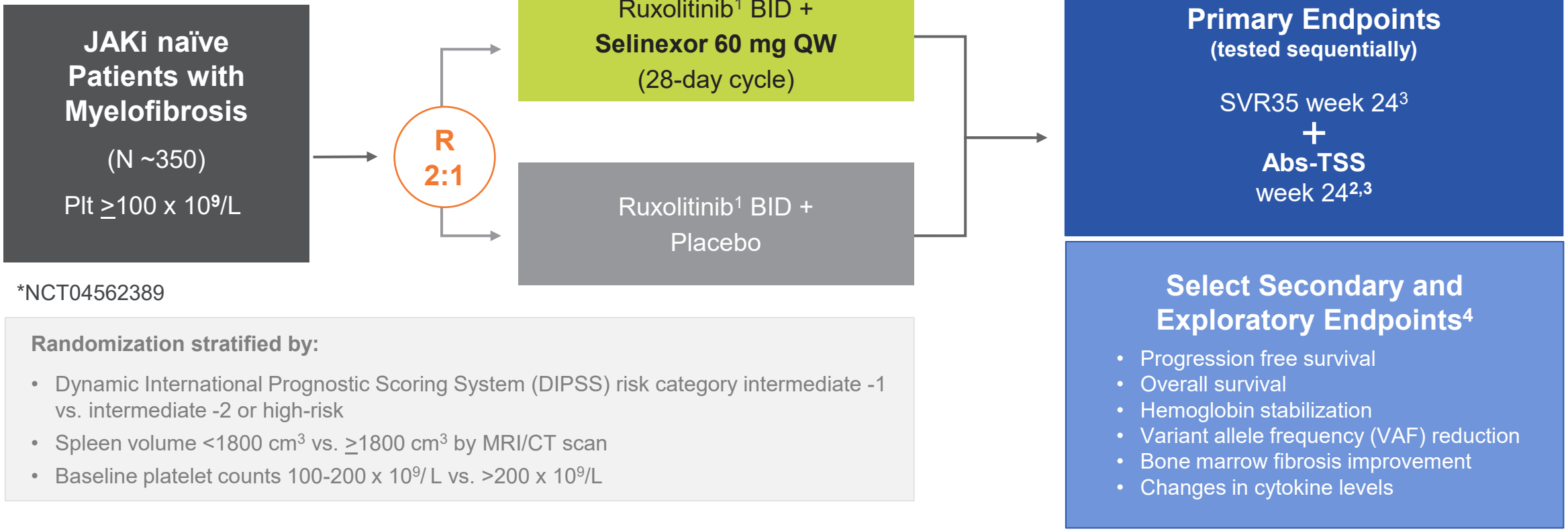
Large safety database with **~30,000 patients treated with selinexor** (CST, IST, and commercial therapies for multiple indications)[7]

* Based on data from multiple clinical trials, including: i) Phase 2 XPORT-MF-035 trial; ii) Phase 2 ESSENTIAL trial, Tantravahi S. et al. SOHO 2024; and, iii) Phase 1 trial evaluating selinexor 60 mg + ruxolitinib in JAKi naïve patients (n=14); Data cut August 1, 2023; Tantravahi S. et al. ASH 2023 Oral Presentation

The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the U.S. FDA or any other regulatory authority for use in myelofibrosis.

1. Ali H, et al. Presented at American Association for Cancer Research Meeting; April 14-19, 2023; Orlando, FL. Poster #CT261. 2. MANIFEST trial. Rampal R, et al. ASCO 2024, abstract 6502; TRANSFORM-1 trial Pemmaraju N, et al. ASH 2023 abstract 620; Harrison et al., COMFORT-II Trial. NEJM. 2012 3. S. K. Tantravahi, et al. Presented at European Hematology Association Congress, June 13-16, 2024. Results from Phase 1 portion of SENTRY trial evaluating selinexor+ ruxolitinib in JAKi naïve patents; data cut August 1, 2023; Average reduction in total symptom score at week 24 relative to baseline, calculated for each evaluable subject. Least square mean of the absolute TSS change was not estimated in the ITT population due to limitations in sample size 4. Ali H., et al. 16th International Congress on Myeloproliferative Neoplasms, October 24–25, 2024. 5. Based on results from the Phase 2 XPORT-MF-035 trial; 6. S.K. Tantravahi, et al. 16th International Congress on Myeloproliferative Neoplasms, October 24–25, 2024, 7. Data on file.

SENTRY (XPORT-MF-034*) Phase 3 Trial of Selinexor in Combination with Ruxolitinib in JAKi Naïve Myelofibrosis



*NCT04562389

Randomization stratified by:

- Dynamic International Prognostic Scoring System (DIPSS) risk category intermediate -1 vs. intermediate -2 or high-risk
- Spleen volume <1800 cm^3 vs. ≥1800 cm^3 by MRI/CT scan
- Baseline platelet counts 100-200 x 10^9/ L vs. >200 x 10^9/L

Top-Line Data Expected March 2026

1. Ruxolitinib dose based on platelet count per prescribing information. 2. Evaluated by myelofibrosis assessment form (MFSAF v4). 3. Both endpoints are powered at >80%; the assumptions for SVR 35 is 40% for ruxolitinib and 70% for selinexor + ruxolitinib; assumptions for abs-TSS are a ≥4-point delta and a standard deviation of 12 for both arms. 4. A sample of secondary and exploratory endpoints to be evaluated. Abs-TSS; absolute TSS; BID: Twice daily; JAKi, janus kinase inhibitors; Plt: Platelet; QW: Once weekly; SVR 35: Spleen volume reduction ≥ 35%:

Preliminary Extrapolated Grade 3+ TEAEs from Blinded Safety Data from Phase 3 SENTRY Trial Point to Potential for Selinexor plus Ruxolitinib to have a More Favorable Safety Profile than Rux Alone[1]

Summary of Treatment Emergent Adverse Events (TEAEs) from Phase 3 SENTRY Trial (2:1 randomization; n= 61)

	Total (N=61) n(%)	
	> 7 months median follow-up	> 12 months median follow-up
At Least One TEAE	59 (96.7)	59 (96.7)
Maximum grade 3 or 4 TEAE	26 (42.6)	33 (54.1)
Serious TEAEs	**11 (18.0)**	**12 (19.7)**
TEAE leading to treatment discontinuation	**2 (3.3)**	**4 (6.6)**

Data cutoff February 2025 for median follow-up of over 7 months
Data cutoff July 2025 for median follow-up of over 12 months

Ruxolitinib Historical[2]	Selinexor + Ruxolitinib Extrapolated from SENTRY[1]
At Least One TEAE 97%	*At Least One TEAE* ~97%
Any Grade 3+ TEAE 57%	*Any Grade 3+ TEAE* ~53%
Serious TEAEs **29%**	***Serious TEAEs*** **~15%**
TEAE leading to treatment discontinuation **6%-11%**	***TEAE leading to treatment discontinuation*** **~5-7%**

1. Data extrapolated from blinded safety data from ongoing Phase 3 SENTRY trial (n=61; data cut-off July 2025) based upon 2:1 randomization, and using historical adverse events rates from ruxolitinib alone. Phase 3 SENTRY trial remains ongoing and the final safety data may differ materially from the extrapolated safety data presented. 2. Source: MANIFEST-2; COMFORT-1.

Rux: Ruxolitinib

Encouraged by the Potential for Lower Rates of Grade 3+ Anemia Based on Preliminary Extrapolated Safety Data on Selinexor plus Ruxolitinib from Blinded Safety Data[1]

Preliminary Blinded Safety Data from Phase 3 SENTRY (2:1 randomization), n= 61

Treatment Emergent Adverse Events (TEAEs), regardless of grade	Total (N=61) n(%)	
	> 7 months median follow-up[3]	> 12 months median follow-up[4]
Patients with At Least One TEAE	59 (96.7)	59 (96.7)
Anemia	33 (54.1)	35 (57.4)
Nausea	**28 (45.9)**	**29 (47.5)**
Thrombocytopenia	24 (39.3)	25 (41.0)
Constipation	18 (29.5)	19 (31.1)
Diarrhoea	12 (19.7)	12 (19.7)
Fatigue	**10 (16.4)**	**12 (19.7)**
Dizziness	10 (16.4)	10 (16.4)
Hypertension	5 (8.2)	8 (13.1)
Pyrexia	6 (9.8)	8 (13.1)
Upper respiratory tract infection	3 (4.9)	8 (13.1)
Alanine aminotransferase increased	5 (8.2)	7 (11.5)
Asthenia	9 (14.8)	7 (11.5)
Decreased appetite	5 (8.2)	7 (11.5)
Vomiting	**6 (9.8)**	**7 (11.5)**
Aspartate aminotransferase increased	5 (8.2)	6 (9.8)
Headache	6 (9.8)	6 (9.8)
Neutropenia	6 (9.8)	6 (9.8)
Blood creatinine increased	4 (6.6)	5 (8.2)
Bone pain	4 (6.6)	5 (8.2)

Grade 3/4 Treatment Emergent Adverse Events

Anemia	**16 (26.2)**	**18 (29.5)**
Thrombocytopenia	**4 (6.6)**	**5 (8.2)**

Ruxolitinib Historical Adverse Event (AE) Data[2]

All grade

Nausea
15%

Fatigue
16%

Vomiting
12%

Grade 3/4

Anemia
37%

Thrombocytopenia
6%

Selinexor + Ruxolitinib Extrapolated AE Rates[1]

All grade

Nausea
~64%

Fatigue
~22%

Vomiting
~11%

Grade 3/4

Anemia
~26%

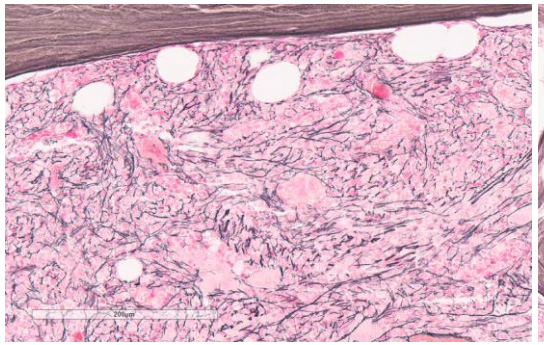
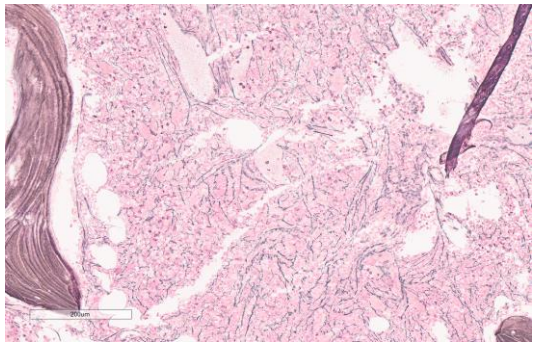
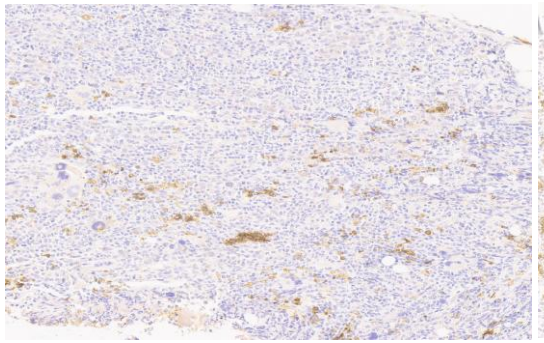
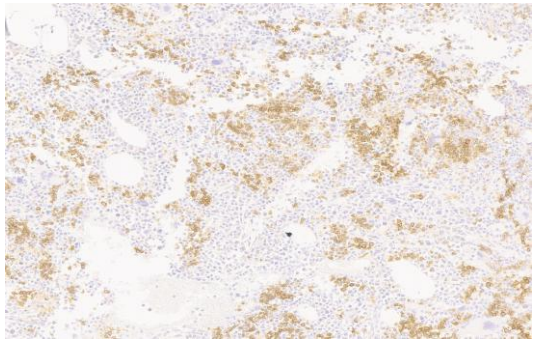
Thrombocytopenia
~9%

1. Data extrapolated from blinded safety data from ongoing Phase 3 SENTRY trial (n=61; data cut-off July 2025) based upon 2:1 randomization, and using historical adverse events rates from ruxolitinib alone. Phase 3 SENTRY trial remains ongoing and the final safety data may differ materially from the extrapolated safety data presented. 2. Source: MANIFEST-2; COMFORT-1. 3. Data cutoff February 2025. 4. Data cutoff July 2025.

Encouraging Evidence of Bone Marrow Modification from Patient Treated with Selinexor plus Ruxolitinib from Phase 1 Portion of SENTRY Trial

Treatment with suboptimal doses of ruxolitinib suggests the potentially fundamental role selinexor may have in myelofibrosis

- Enrolled on selinexor 60 mg + ruxolitinib 15 mg twice a day (per label); ruxolitinib dose decreased to 5 mg twice a day due to toxicity in cycle 2.
- Achieved an SVR35 as early as week 12 and TSS50 achieved as early as week 8
- Baseline TSS was 42 and 19.5 at week 8

	Pre-treatment	Week 24
Reticulin **46% reduction in fiber density**[1,2]		
CD71+ Erythroid Progenitors **197% increase in CD71+ cells**[1,2]		

1. Data presented by Haris Ali et al. in poster presented October 2024 at the International Congress on Myeloproliferative Neoplasms titled "Selinexor-Driven Regulation of Proinflammatory Cytokines May Lead to Stabilization of Hematologic Parameters and Bone Marrow Function in Patients With Myelofibrosis: Case Studies From the Phase 1 SENTRY Trial". 2. Assessed by digital pathology

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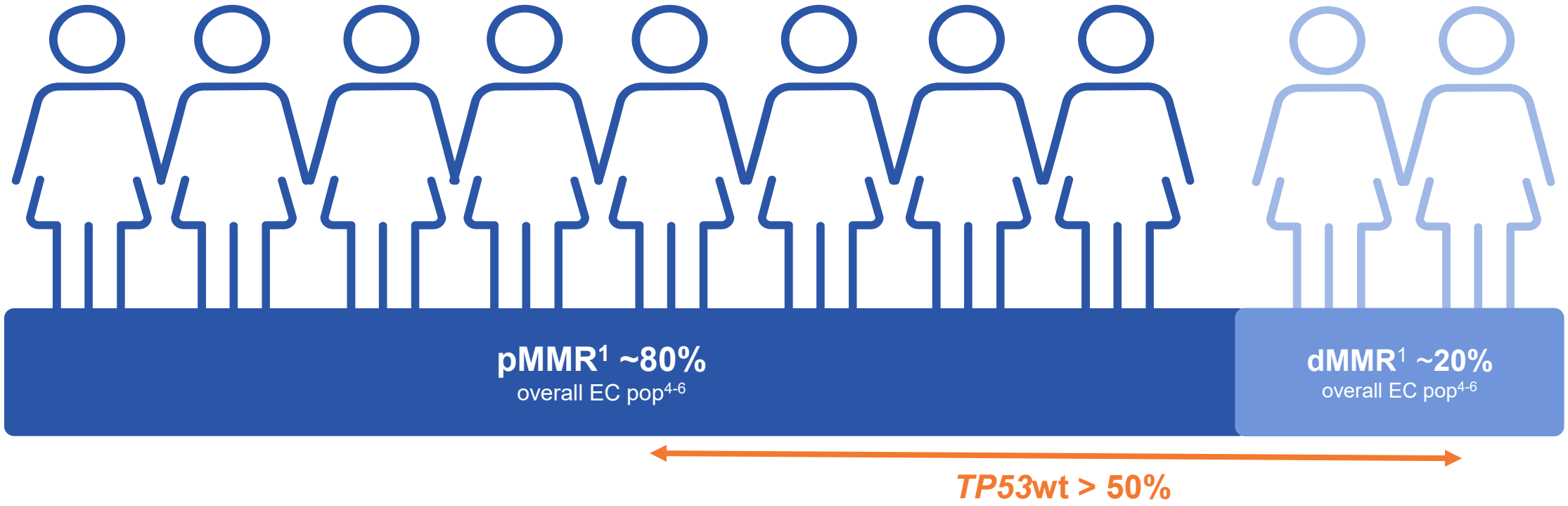
ENDOMETRIAL CANCER

Karyopharm® Therapeutics

Focusing Phase 3 XPORT-EC-042 Trial on Patients with *TP53*wt EC that are pMMR or dMMR and Medically Ineligible to Receive a Checkpoint Inhibitor



Molecular characterization is used to inform treatment decisions for patients with EC, yet there are currently no approved therapies specifically targeting *TP53*wt EC patients[1-3]

The safety and efficacy of selinexor in endometrial cancer has not been established and has not been approved by the U.S. FDA or any other regulatory authority for use in endometrial cancer.

EC, endometrial cancer; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair; TP53, tumor protein 53 gene; wt, wild-type

1. Tronconi F, et al. Crit Rev Oncol Hematol. 2022;180:103851. 2. Levine DA. Nature. 2013;497(7447):67–73. 3. Oaknin A, et al. Ann Oncol. 2022;33:860-877. 4. Leslie KK, et al. Gynecol Oncol. 2021;161(1):113-121. 5. Mirza MR, et al. Presentation at: ESMO Congress; October 20-24, 2023. 6. Vergote I, et al. Presentation at: European Society for Medical Oncology Virtual Plenary; March 17-18, 2022; Abstract VP2-2022; Vergote I, et al J Clin Oncol. 2023;41(35):5400-5410.

Updated XPORT-EC-042* Phase 3, Randomized, Double-Blind Trial of Selinexor as Maintenance Therapy for Patients with *TP53*wt, Advanced or Recurrent EC[1]

TP53 Wild-Type Status is Assessed by Companion Diagnostic Partner Foundation Medicine[2]

Study is Actively Enrolling in Collaboration with ENGOT[3] and GOG[4]

Planned Enrollment
(n ~276)

Patients aged ≥18 years with
- Known *TP53*wt EC by central NGS[1]
  - Patients w/ *TP53*wt/dMMR tumors must be medically ineligible to receive checkpoint inhibitors
- Primary Stage IV disease or first recurrent EC
- Received ≥12 weeks of platinum-based chemotherapy ± immunotherapy

R
1:1

Selinexor 60 mg orally QW
Until PD, toxicity, or 3 years
(n ~138)

Placebo orally QW
Until PD, toxicity, or 3 years
(n ~138)

Primary Endpoint[5]:
- PFS assessed by investigator

PFS mITT (n ~220)[6]

PFS ITT (n ~276)[6]

Populations tested sequentially

Secondary endpoints remain unchanged

*NCT05611931

The safety and efficacy of selinexor in endometrial cancer has not been established and has not been approved by the U.S. FDA or any other regulatory authority.

Randomization stratified by:
- Response upon completion of platinum-based therapy: CR vs. PR
- Primary stage IV vs recurrent EC

Patient populations defined as:
- mITT population: A/R EC patients whose tumors are a) *TP53*wt/non-MSI-H (pMMR) EC, or b) A/R EC patients whose tumors are *TP53*wt/MSI-H (dMMR) and medically ineligible to receive checkpoint inhibitors
- ITT population A/R EC patients whose tumors are *TP53*wt

Top-line data anticipated in mid-2026

A/R, advanced/recurrent; PFS, progression-free survival; PD, progressive disease; QW, every week; NGS, Next Generation Sequencing. 1. Based on the new proposed study design; amendment incorporating these changes has been submitted to FDA; 2. Utilizing Foundation Medicine's tissue-based comprehensive genomic profiling test to identify TP53 status. 3. European Network for Gynaecological Oncological Trial groups. 4. Gynecologic Oncology (GOG) Foundation. 5. The primary PFS analysis will be triggered once 101 PFS events have been observed in the mITT population. 6. mITT and ITT are powered >80% based upon a one-sided alpha of 0.025 and a target PFS HR of 0.55. Median PFS times for the placebo and selinexor arms are assumed to be 5.0 and 9.1 months, respectively.

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MULTIPLE MYELOMA

Karyopharm® Therapeutics

Phase 3 Global Study (XPORT-MM-031/ EMN29[1])* Evaluating SPd in Patients with Previously Treated Multiple Myeloma

Enrollment Complete (n ~120)[2]

Patients with Pomalidomide-naïve RRMM

1-4 prior therapies including a PI, lenalidomide; and an anti-CD38 mAb as part of the last line of therapy prior to enrollment

R 1:1

SPd (n ~60)

SEL: 40 mg[3] QW PO D1, 8, 15 and 22

POM: 4 mg QD PO (D1-21)

DEX: 40 mg PO D1, 8, 15 and 22

28-day cycle

EPd (n ~60)

ELOTUZUMAB (Elo): 10 mg/kg IV (Days 1, 8, 15 and 22 for cycles 1-2); 20 mg/kg IV (Day 1 for cycles ≥ 3)

POM: 4 mg QD PO (D1-21)

DEX: 40 mg PO D1, 8, 15 and 22

28-day cycle

Primary Endpoint

PFS

*NCT05028348

The safety and efficacy of SPd has not been established and has not been approved by the FDA or any other regulatory authority.

Top-line data anticipated in 1H-2026

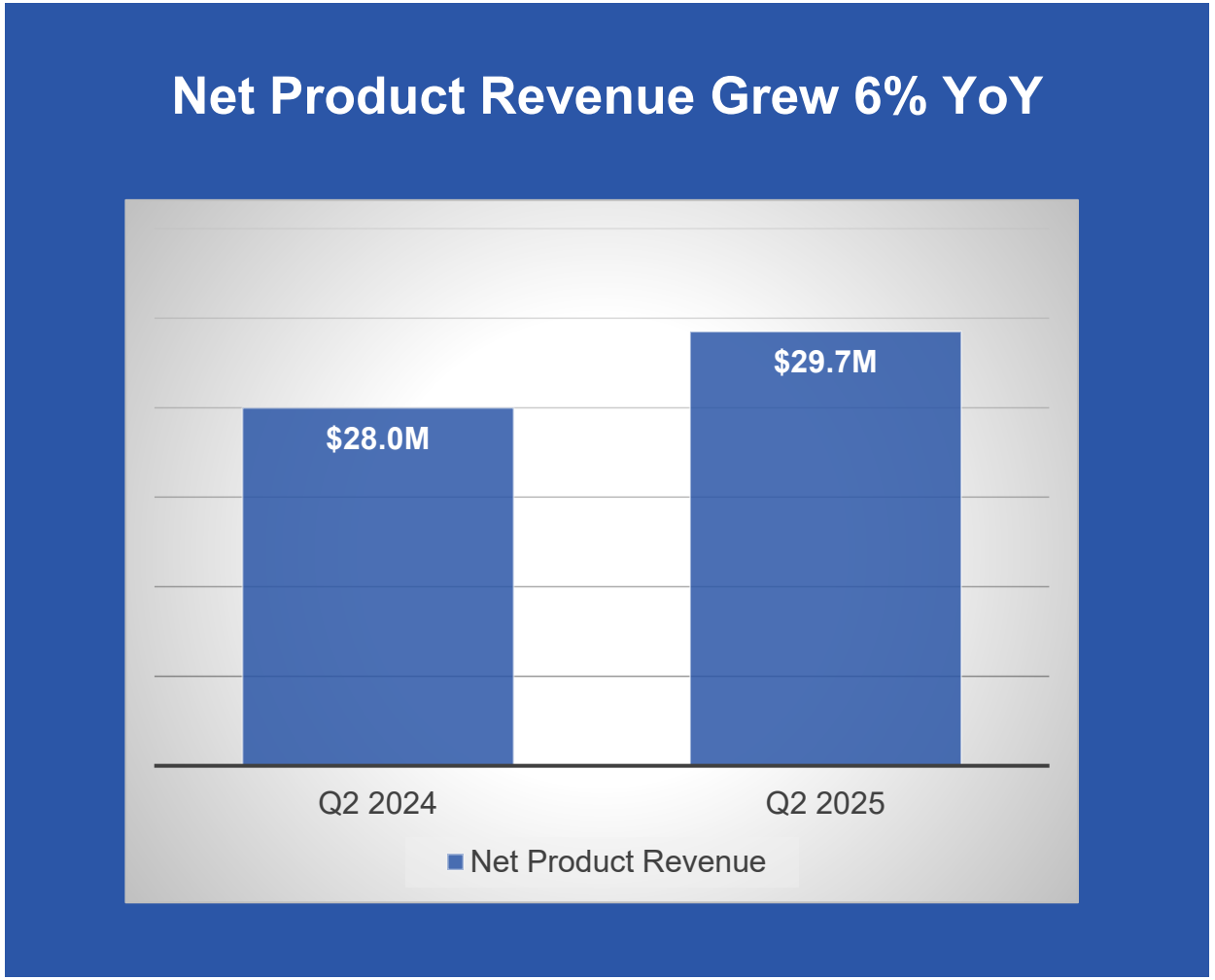
PI: proteasome inhibitor; mAB: monoclonal antibody; SPd: selinexor plus pomalidomide and dexamethasone

1.Sponsored by European Myeloma Network (EMN). 2. Per amended protocol. 3. 40 mg selinexor dose was based upon evaluation of the safety and benefit of selinexor 40 and 60 mg doses in combo with Pd observed in the STOMP and 028 studies.

COMMERCIAL HIGHLIGHTS

Sohanya Cheng
Chief Commercial Officer and Head of Business Development

Commercial Highlights



Q2 2025 Highlights

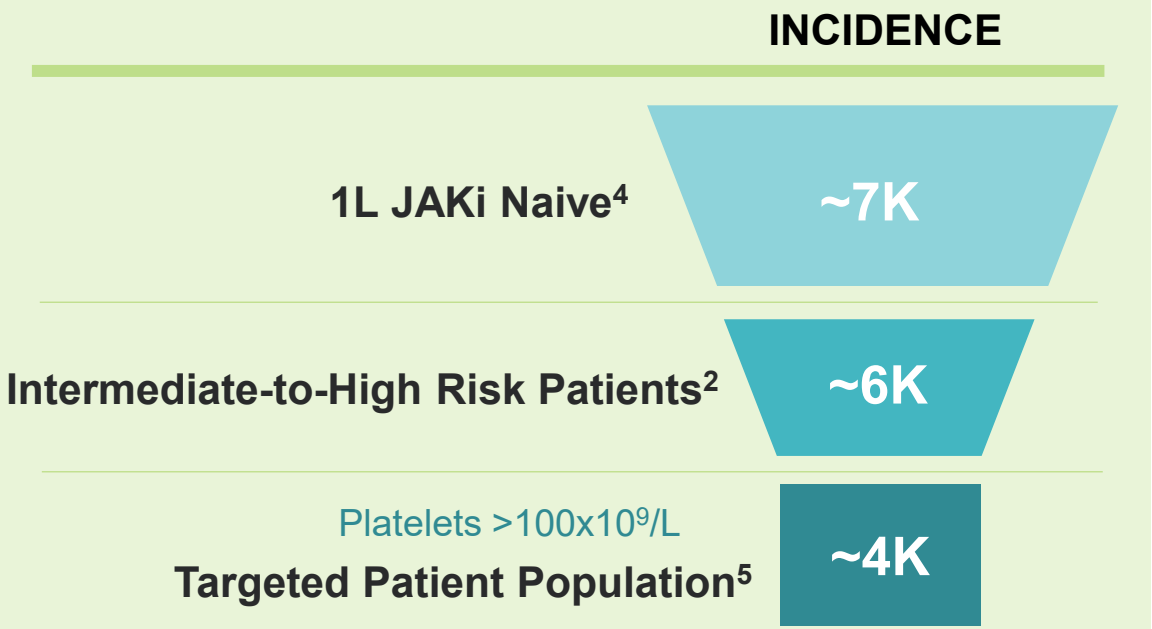
- U.S. net product revenue was $29.7 million in 2Q’25, up 6% from $28.0 million in 2Q’24.
- Demand for XPOVIO was consistent in 2Q’25 compared to 2Q’24, with the community setting continuing to drive approximately 60% of overall U.S. net product revenue
- Myeloma market remains highly competitive
- Net product revenue guidance range of $110M-$120M for full year 2025
- Preparing for rapid and successful launch in myelofibrosis, pending regulatory approval, with the Company’s established commercial organization

Selinexor has the Potential to Deliver Up to ~$1 Billion in Annual U.S. Peak Revenue[1] as the First Approved Combination Therapy in JAKi Naïve Myelofibrosis

Global Market Prevalence

- ✓ **~ 20,000** living with MF in the U.S.[2]
- ✓ **~17,000** living with MF in the EU[2]
- ✓ **JAK inhibitors** are the **only** approved class of therapy
- ✓ Ruxolitinib generates **>$1 billion**[3] of revenues annually in the U.S in myelofibrosis

Newly Diagnosed Patients in the U.S. Annually



Up to ~$1B Annual U.S. Peak Revenue Opportunity[4,6]
Plus Global Ex-U.S. Royalties and Milestones

1. Annual U.S. peak revenue opportunity is not guidance, but instead represents what the Company believes to be Karyopharm's peak revenue opportunity, if approved, based on internal estimates, including market research. 2. Clarivate/DRG (2023). 3. Incyte 2Q'25 earnings presentation. 4. 2032 estimates based on Clarivate/DRG (2023) and Epic Oncology (2021); janus kinase inhibitor (JAKi). 5. Internal Company estimates. 6. Pending positive data from the Phase 3 SENTRY trial and regulatory approval.

Well-Positioned for a Rapid and Successful Launch as Potentially the First Approved **Combination Therapy in Myelofibrosis**[1]

Significant Need to Improve SoC

Less than half of patients achieve SVR35 or meaningful symptom improvement with the current standard of care[2]

75%[3] **of U.S. physicians** surveyed indicated **intent to adopt combination therapy**

Opportunity for Novel MoA: JAK inhibition is the sole mechanism that has been approved

Compelling Target Product Profile

First to market combination

Nearly 80% achieve rapid, deep and sustained spleen reduction with selinexor; robust and sustained symptom improvement observed[4]

~30,000 patients treated with selinexor across multiple indications with well-established safety profile

Once-weekly, 60 mg dose, combined with prophylactic dual anti-emetics, expected to improve safety profile

Synergistic Customer Base

~80% overlap between targeted myelofibrosis and existing multiple myeloma accounts **in the community**, allows for strong field synergies

60% to 70% of myelofibrosis patients are treated **in the community** setting[5]

Experienced Cross-Functional Hematology Team

Strong commercial capabilities in Sales, Marketing and Market Access to **drive a rapid launch**

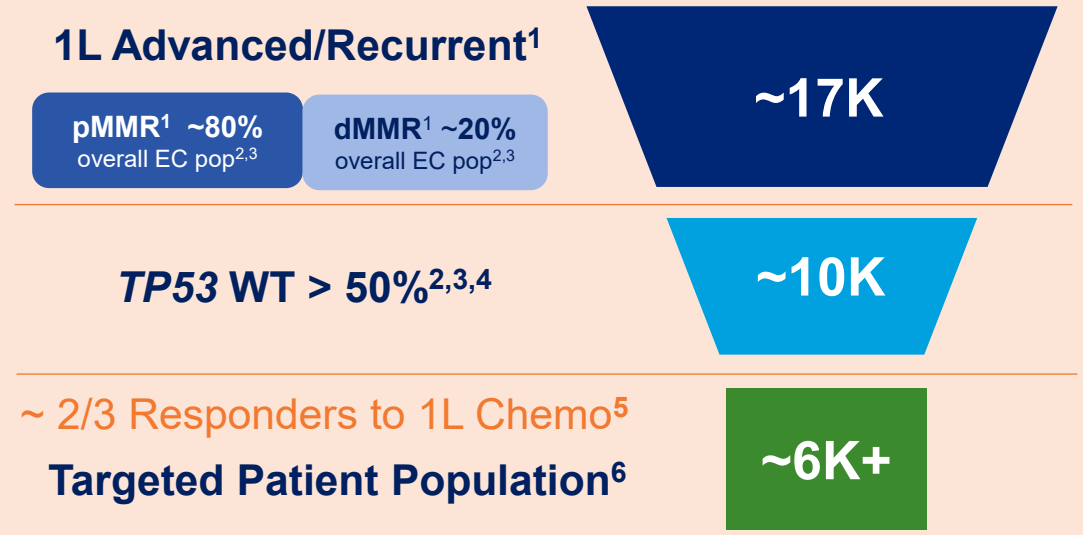
Established patient support hub enabling optimal patient access

Experienced Medical Affairs team to support strong KOL engagement

1. Pending positive data from the Phase 3 SENTRY trial and regulatory approval. 2. MANIFEST and TRANSFORM Phase 3 studies. 3. Data on file qualitative market research May 2023, N =25 MF treaters US hem onc and med oncs.
4. Based on results from Phase 1 trial evaluating selinexor 60 mg + ruxolitinib in JAKi naïve patients (n=14). 5. Compass claims data 2024.

Endometrial Cancer: Potential to be the First Novel Oral Maintenance Therapy in *TP53* Wild-Type Endometrial Cancer

Addressable Market Opportunity in the U.S.



Key Commercial Success Factors

1. **First novel, biomarker-specific oral** maintenance therapy[7]
2. **~80% customer overlap in the Community MM accounts[8]**
3. Anticipated rapid launch, if approved, with experienced **commercialization capabilities** including field, market access and MSLs

The safety and efficacy of selinexor in endometrial cancer has not been established and has not been approved by the U.S. FDA or any other regulatory authority.

1. Clarivate/DRG Endometrial Carcinoma Epidemiology Dashboard 2032 estimates (2023). 2. Mirza, M et al. (2023, October 2024). Dostarlimab + Chemotherapy for the Treatment of Primary Advanced or Recurrent Endometrial Cancer: Analysis of Progression Free Survival and Overall Survival Outcomes by Molecular Classification in the ENGOT-EN6-NSGO/GOG-3031/RUBY Trial. [Conference presentation]. ESMO 2023 Congress, Madrid, Spain. 3. Mutated p53 portends improvement in outcomes when bevacizumab is combined with chemotherapy in advanced/recurrent endometrial cancer: An NRG Oncology study, Leslie, Kimberly K. et al. Gynecologic Oncology, Volume 161, Issue 1, 113 – 121 3. 4. Vergote I, et al J Clin Oncol. 2023;41(35):5400-5410. 5. Makker, V et al. (June 2024). Long-term Follow-up of Selinexor Maintenance for Patients With TP53WT Advanced or Recurrent Endometrial Cancer: A Prespecified Subgroup Analysis From the Phase 3 ENGOT-EN5/GOG-3055/SIENDO Study [Conference presentation]. ASCO 2024 Congress. 5400-5410; Mirza MR, et al. SGO 2023; JEMPERLI Prescribing Information. 6.Internal Company estimates with landscape Ph 3 trials. 7. Pending positive data from the XPORT-EC-042 trial and regulatory approval. 8. Internal claims data analysis of MM and EC target list.

FINANCIAL HIGHLIGHTS

Lori Macomber, CPA
Chief Financial Officer and Treasurer

Q2 2025 Financial Results and Guidance

Statements of Operations ($ millions)	2Q 2025	2Q 2024
Total Revenue	**$37.9**	**$42.8**
XPOVIO Net Product Revenue	29.7	28.0
License and Other Revenue	8.2	14.8
Total Operating Expenses	**$62.3**	**$70.9**
Cost of Sales	1.1	1.5
Research and Development Expenses	32.8	38.4
Selling, General & Administrative Expenses	28.5	31.1
Other (Expense) Income, net	**$(12.8)**	**$52.0**
Net (Loss), Income	**$(37.3)**	**$23.8**
Basic Net (Loss) Income per share	**$(4.32)**	**$2.26**
Diluted Net Loss per share	**$(4.32)**	**$(2.97)**

Balance Sheet ($ millions)	June 30, 2025	Dec 31, 2024
Cash, Cash Equivalents, Restricted Cash & Investments	**$52.0**	**$109.1**

Note: Figures may not sum due to rounding. All share amounts and per share amounts in this presentation have been adjusted to reflect a 1-for-15 reverse split of our common stock, which we effected on February 25, 2025.

2025 Financial Guidance

- Total Revenue of **$140-$155** million
- U.S. XPOVIO Net Product Revenue of **$110-$120** million
- R&D and SG&A Expenses of **$240-$250** million

The Company expects its existing liquidity, including the revenue it expects to generate from XPOVIO net product sales and its license agreements, will be sufficient to fund its planned operations to the maturity of its senior convertible notes due October 2025 (Remaining 2025 Notes). Excluding the $24.5 million Remaining 2025 Notes maturity and its $25.0 million minimum liquidity covenant, the Company expects it would have sufficient liquidity to fund planned operations into January 2026.

CLOSING REMARKS

Richard Paulson
President and Chief Executive Officer

Exploring Financing Transactions and Strategic Alternatives to Extend Cash Runway, Maximize Value and Deliver on Potentially Transformative Opportunities

Maintain the Company's **Profitable Commercial Foundation** in the Competitive Multiple Myeloma Marketplace

Report Top-Line Results from the Phase 3 SENTRY Trial in March 2026; Potentially Transformative Opportunity to Define a New Treatment Paradigm in Myelofibrosis

Report Top-Line Results from the Phase 3 XPORT-EC-042 Trial in mid-2026; Potentially Transformative Opportunity to Be First Maintenance-Only Therapy in Endometrial Cancer

Complete Enrollment of Pivotal, Phase 3 SENTRY Trial in Myelofibrosis

Report Top-Line Results from the Phase 3 XPORT-MM-031 Trial in multiple myeloma in 1H'26

BELIEVERS IN THE EXTRAORDINARY

APPENDIX

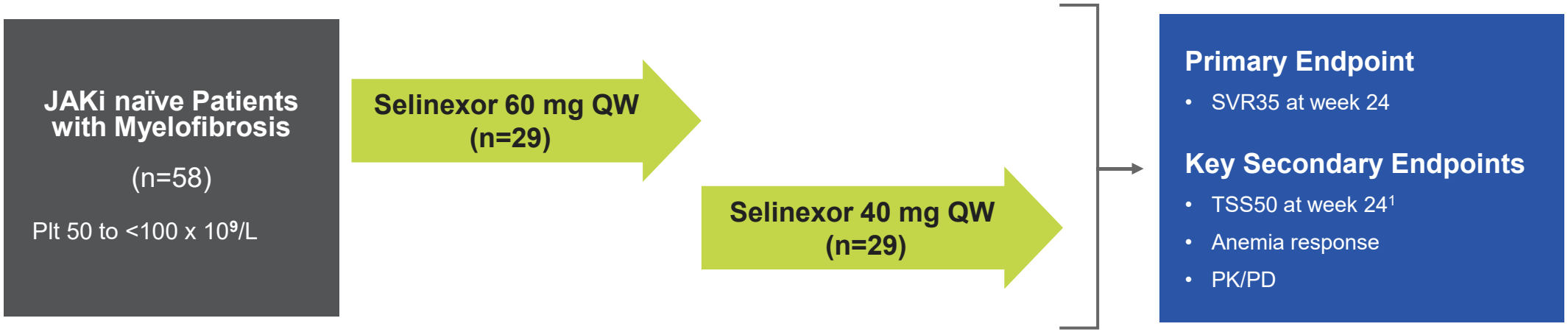
Focused High Potential Pipeline – Our Top Strategic Priority for 2025 is High-Quality Clinical Trial Execution on our Phase 3 SENTRY Trial in MF

	Indication	Early Stage	Mid Stage	Late Stage	Commercial
XPOVIO® (selinexor)	Multiple myeloma (penta-refractory) w/dexamethasone				
	Multiple myeloma (2L+) w/bortezomib + dexamethasone				
	DLBCL (R/R) Monotherapy				
SELINEXOR	**Myelofibrosis (JAKi naïve)** — Topline Data Expected March 2026				
	Endometrial cancer (maintenance; *TP53* wild-type)				
	Multiple myeloma (2L+ post-anti CD38) [1]				
	DLBCL (R/R) [2]				
ELTANEXOR[3]	TBD				
KPT-9274[3]	Rhabdomyosarcoma / Ewings Sarcoma				
KPT-350[3]	TBD				

hematologic cancer solid tumor cancer

1. EMN29 Study: Sponsored by European Myeloma Network. 2. XPORT-DLBCL-030 is a Phase 2/3. 3. Further development of the Company's early-stage pipeline is currently paused in line with prioritization of late-stage pipeline programs.

SENTRY-2 (XPORT-MF-044*) Phase 2 Trial Evaluating Selinexor As Monotherapy in JAKi Naïve MF Patients with Lower Platelet Counts



* NCT05980806

Optional Add-on Medications	
Week 12 if SVR <10%	**Week 24 if SVR <35%**
Add **ruxolitinib**[2]**:** if plt >50 x 10^9/L, and hemoglobin level is ≥ 10 g/dL	
Add **pacritinib:** if plt <50 x 10^9/L	
Add **momelotinib**[3] if plt >50 x10^9/L hemoglobin level is <10 g/dL	

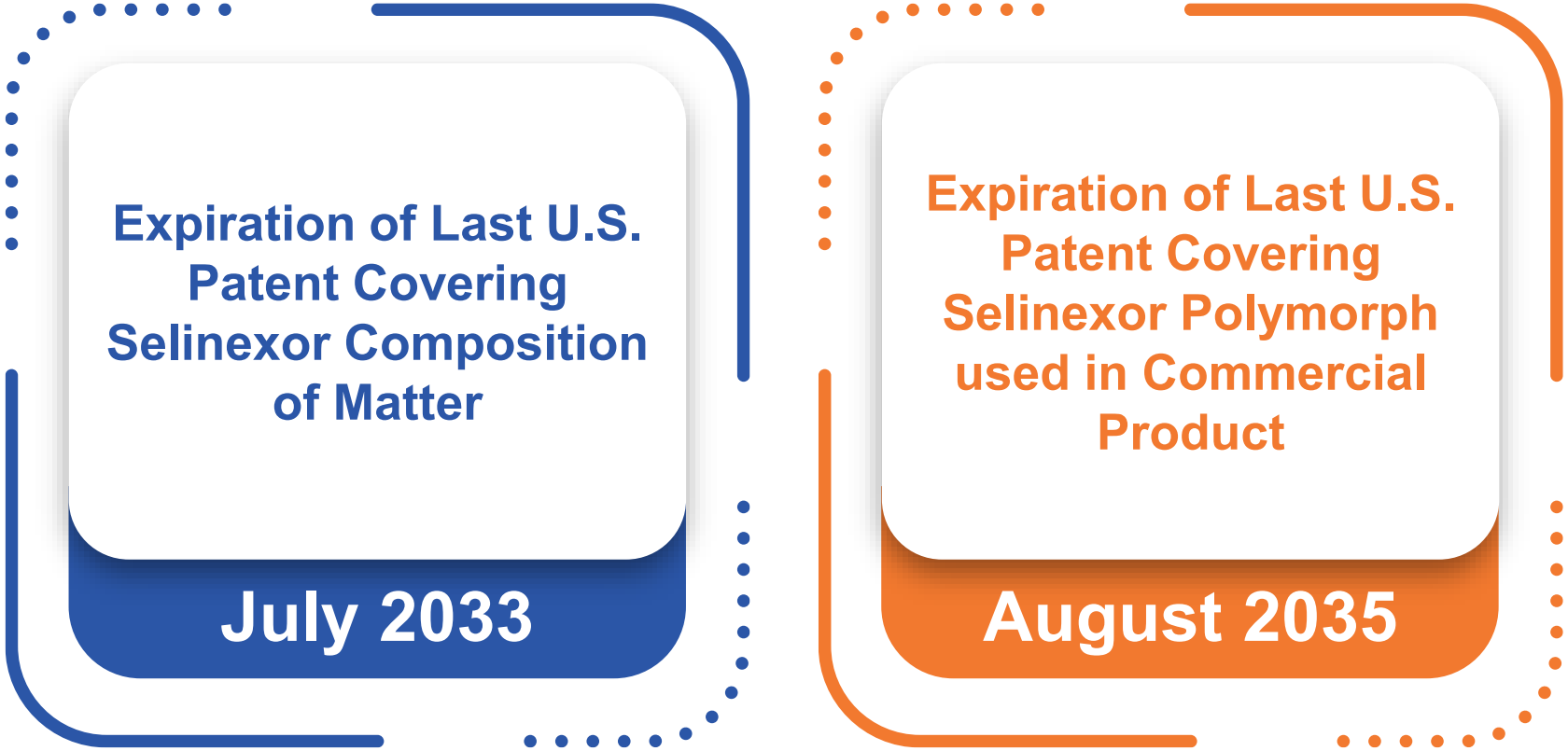
SOBI[4]

Pacritinib supply agreement with SOBI

The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the U.S. FDA or any other regulatory authority for use in myelofibrosis.

1. Evaluated in the myelofibrosis assessment form (MFSAF) 2. Ruxolitinib dose based on platelet count per prescribing information 3.In the U.S. only 4. For supply of pacritinib
Plt: platelet; QW: Once weekly; SVR 35: Spleen volume reduction ≥ 35%; TSS50: Total symptom score reduction of ≥50%; PD: pharmacodynamic; PK: Pharmacokinetic

Intellectual Property – Selinexor Protected by Global Patent Portfolio



Note: Selinexor's ex-U.S. patents will expire no earlier than 2032

Total Symptom Score Evaluation - MFSAF v4 Questionnaire

Domains	Questions	Scoring Scale
Fatigue	1. During the past 24 hours, how severe was your worst **fatigue** (weariness, tiredness)?	(symptom absent) 0-10 (worst)
Night Sweats	2. During the past 24 hours, how severe was your worst **night sweats** (or feeling hot of flushed)?	(symptom absent) 0-10 (worst)
Itching	3. During the past 24 hours, how severe was your worst **itching**?	(symptom absent) 0-10 (worst)
Abdominal Discomfort	4. During the past 24 hours, how severe was your worst **abdominal discomfort** (feeling pressure or bloating)?	(symptom absent) 0-10 (worst)
Pain under left ribs	5. During the past 24 hours, how severe was your worst **pain under your ribs** on your left side?	(symptom absent) 0-10 (worst)
Fullness	6. During the past 24 hours, what was the worst feeling of **fullness** you had after beginning to ear?	(symptom absent) 0-10 (worst)
Bone Pain	7. During the past 24 hours, how severe was your worst **bone pain** (not joint or arthritis pain)?	(symptom absent) 0-10 (worst)