



Fourth Quarter and Full Year 2022 Financial Results & Business Update

February 15, 2023

On Today's Call

- **Welcome**

Elhan Webb, CFA, *Senior Vice President, Investor Relations*

- **Overview**

Richard Paulson, *President and Chief Executive Officer*

- **Commercial Highlights**

Sohanya Cheng, *Chief Commercial Officer*

- **Pipeline Update**

Dr. Reshma Rangwala, *Chief Medical Officer*

- **Financial Summary and Guidance**

Michael Mason, *Chief Financial Officer*

- **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 2023 total revenue, 2023 U.S. net product revenue and 2023 non-GAAP R&D and SG&A expenses; Karyopharm's expected cash runway; the ability of selinexor or eltanexor to treat patients with multiple myeloma, endometrial cancer, myelofibrosis, myelodysplastic neoplasms, diffuse large B-cell lymphoma, and other diseases; expectations related to future clinical development and potential regulatory submissions of selinexor or eltanexor; expectations with respect to commercialization efforts; submissions to, and the review and potential approval of selinexor, eltanexor or any of its other product candidates by, regulatory authorities, including the Company's regulatory strategy, the anticipated availability of data to support such submissions, timing of such submissions and actions by regulatory authorities and the potential availability of accelerated approval pathways; the expected design of the Company's clinical trials; and the therapeutic potential of and potential clinical development plans for Karyopharm's product candidates, especially selinexor and eltanexor. 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 and eltanexor, 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 risk that the COVID-19 pandemic could disrupt Karyopharm's business more severely than it currently anticipates, including by negatively impacting sales of XPOVIO, interrupting or delaying research and development efforts, impacting the ability to procure sufficient supply for the development and commercialization of selinexor or other product candidates, delaying ongoing or planned clinical trials, impeding the execution of business plans, planned regulatory milestones and timelines, or inconveniencing patients; 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 trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; 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 studies; 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; development or regulatory approval of drug candidates by Karyopharm's competitors for products or product candidates in which Karyopharm is currently commercializing or developing; 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 September 30, 2022, which was filed with the Securities and Exchange Commission (SEC) on November 3, 2022, 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 and eltanexor are investigational drugs that have not been approved by the FDA or any other regulatory agency, and the safety and efficacy of these drugs has not been established by any agency.

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Richard Paulson
Chief Executive Officer

OVERVIEW



Innovation and Patient Focused

Founded in 2008, building on over a decade of research into selective inhibition of nuclear export (SINE) as a novel mechanism of action



Passionately driven in its mission to positively impact lives and defeat cancer

Positioned for Next Stage of Growth



XPOVIO / NEXPOVIO

Approved in Multiple Myeloma (MM) and DLBCL¹

- Expanded global footprint with regulatory approvals in 40 countries
- Generated total revenues of \$157M in 2022
- Moving into earlier lines of therapy in MM

Focused Clinical Pipeline with One Planned and Two Ongoing Pivotal Studies; Optimizing Dose for Efficacy and Tolerability

- Phase 3 selinexor+ruxolitinib in treatment-naïve MF (planned)²
- Phase 3 SPd³ in R/R MM post anti-CD38
- Phase 3 selinexor as maintenance in *TP53* wild-type EC⁴

Strong Financial Position

- Cash position of \$280M⁵ at end of 2022
- Cash runway until late 2025

Key Program Accomplishments in 2022

Multiple Myeloma

Grew U.S. XPOVIO net sales by 22% to \$120.4M

- Received full marketing authorization in the EU for NEXPOVIO; Approved in 40 countries
- Commercial launches by partners ex-US
- Initiated pivotal Phase 3 study evaluating lower dose selinexor, SPd¹, an all oral regimen in R/R MM

Endometrial Cancer

Initiated pivotal Phase 3 study of selinexor as a maintenance therapy in *TP53* wild-type EC

- Partnership with Foundation Medicine to develop TP53 companion diagnostic
- Presented top-line and subgroup analysis data from SIENDO study in EC

Myelofibrosis

Initial results from Phase 1 study evaluating selinexor+ruxolitinib in treatment-naïve MF

- Encouraging preliminary results across the three relevant endpoints of SVR35², TSS50³ and hemoglobin stabilization

Myelodysplastic Neoplasms

Completed recruitment for interim analysis of Phase 2 study evaluating eltanexor in high-risk relapsed/refractory MDS

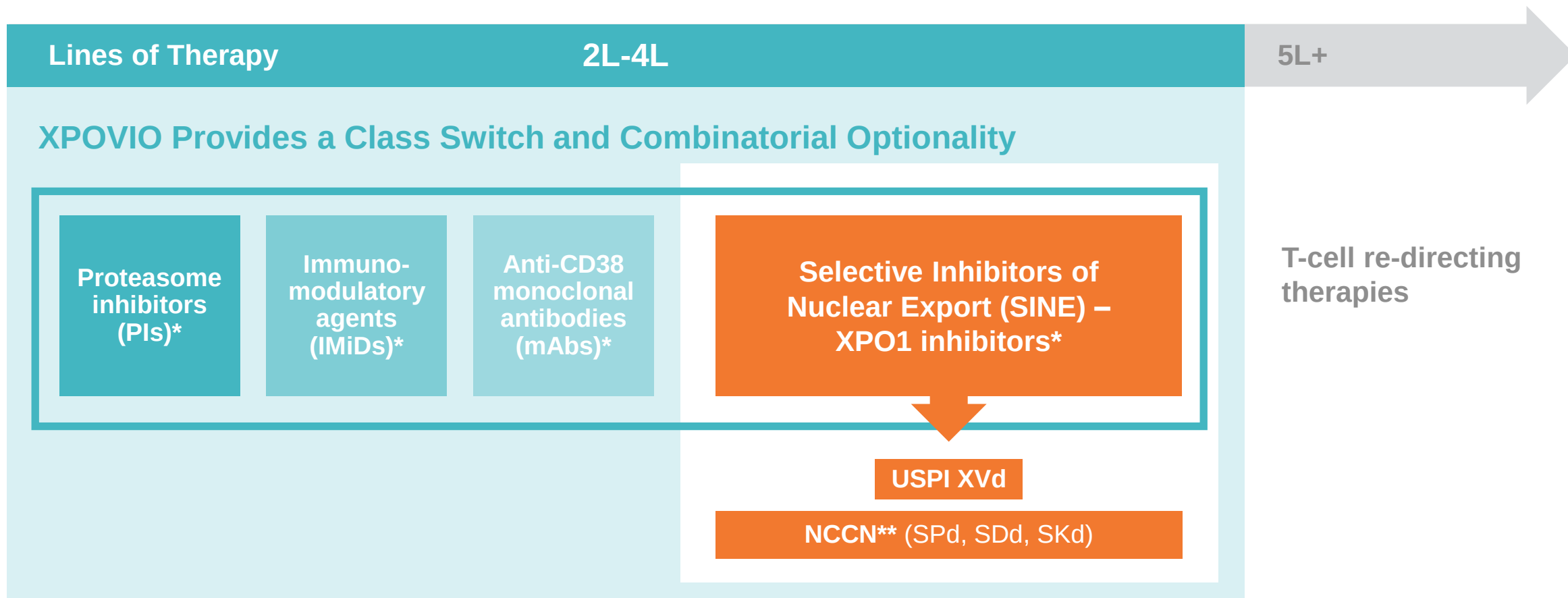
- Evaluating eltanexor, second SINE compound, in patients with high unmet need

Sohanya Cheng
Chief Commercial Officer

COMMERCIAL HIGHLIGHTS



XPOVIO: Novel Class of Therapy and Convenient Oral Treatment for 2L–4L RRMM post anti-CD38

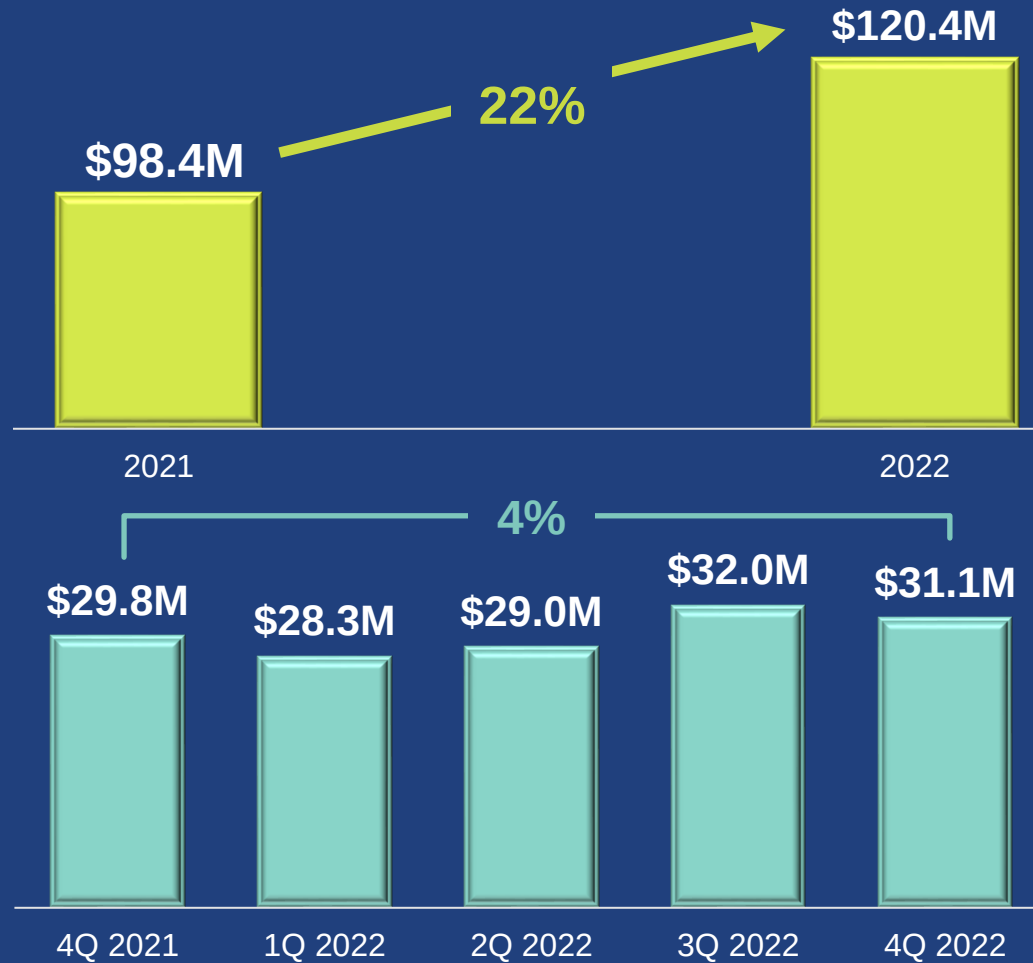


XPOVIO combinations other than XVd and Xd will not be promoted by Karyopharm, but may be considered for future indication updates.

Safety and efficacy of selinexor in combinations other than XVd and Xd have not been established and have not been approved by the US FDA or any other regulatory authority.

XPOVIO Update: 4Q 2022 and FY 2022

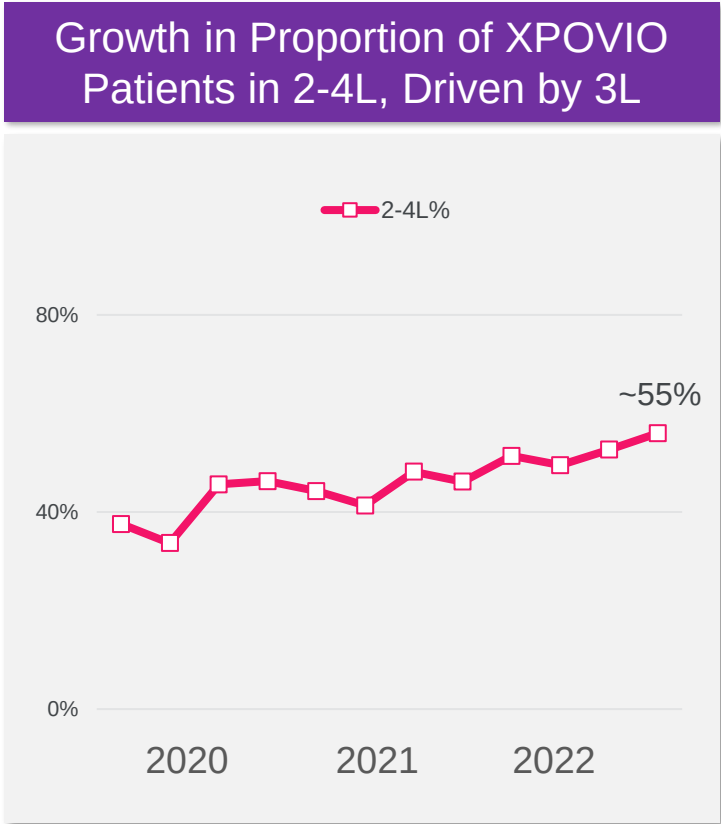
U.S. Net Product Revenue up 22% YoY Driven by Growth in 2L-4L



4Q and FY 2022 Highlights

- Delivered \$120.4M for FY 2022 vs 2021, representing 22% YoY growth
- FY 2022 demand growth driven primarily by new starts and refills
- Community sales grew 28% in FY 2022 vs 2021 and contributed to ~70% of selinexor revenues in Q4 2022
- Academic sales grew 7% in FY 2022 vs 2021, despite increased competition in Q4 2022
- Continued shift into earlier lines of therapy with ~55% of patients in 2-4L¹, and increase in duration of therapy YoY
- Continued improvement in perception and intent-to-prescribe data in 2-4L²

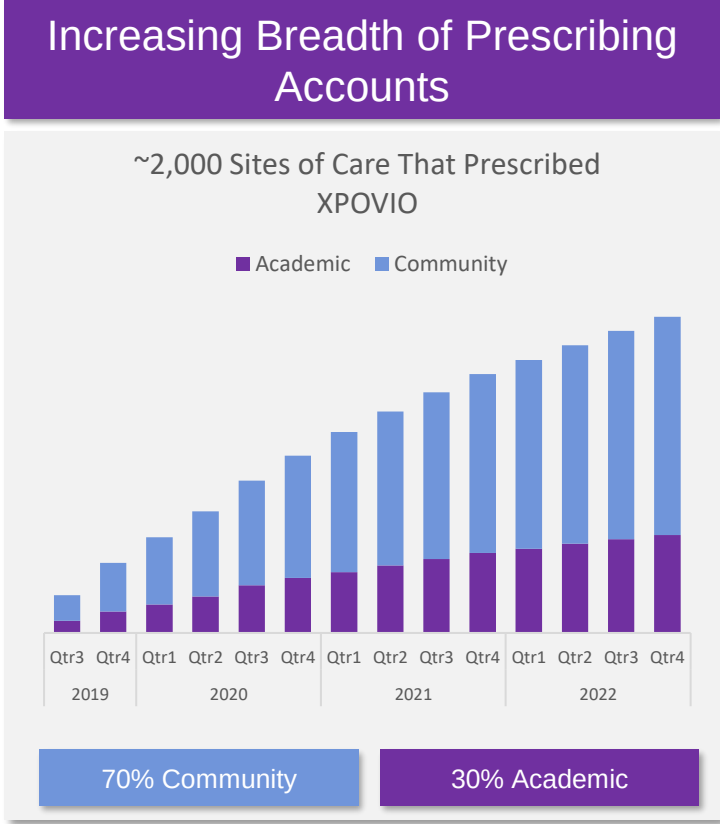
XPOVIO: Continued Progress Across Key Growth Drivers



Source: KOMODO NRx All Claims. *Partial Q4 data and subject to restatements

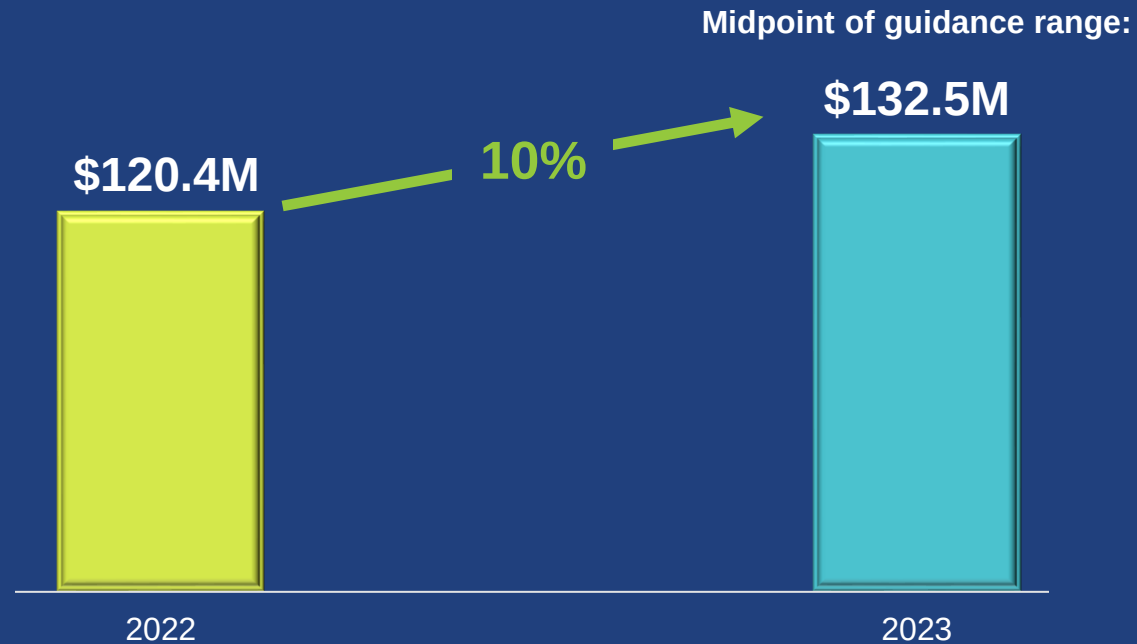


Source: Internal Specialty Pharmacy (SP) data. Based on new starts in 1H 2022 vs. 1H 2021



Source: Veeva and SP / Specialty Distributor data

XPOVIO to Drive Double Digit Growth in Net Sales in 2023



2023 Growth Drivers

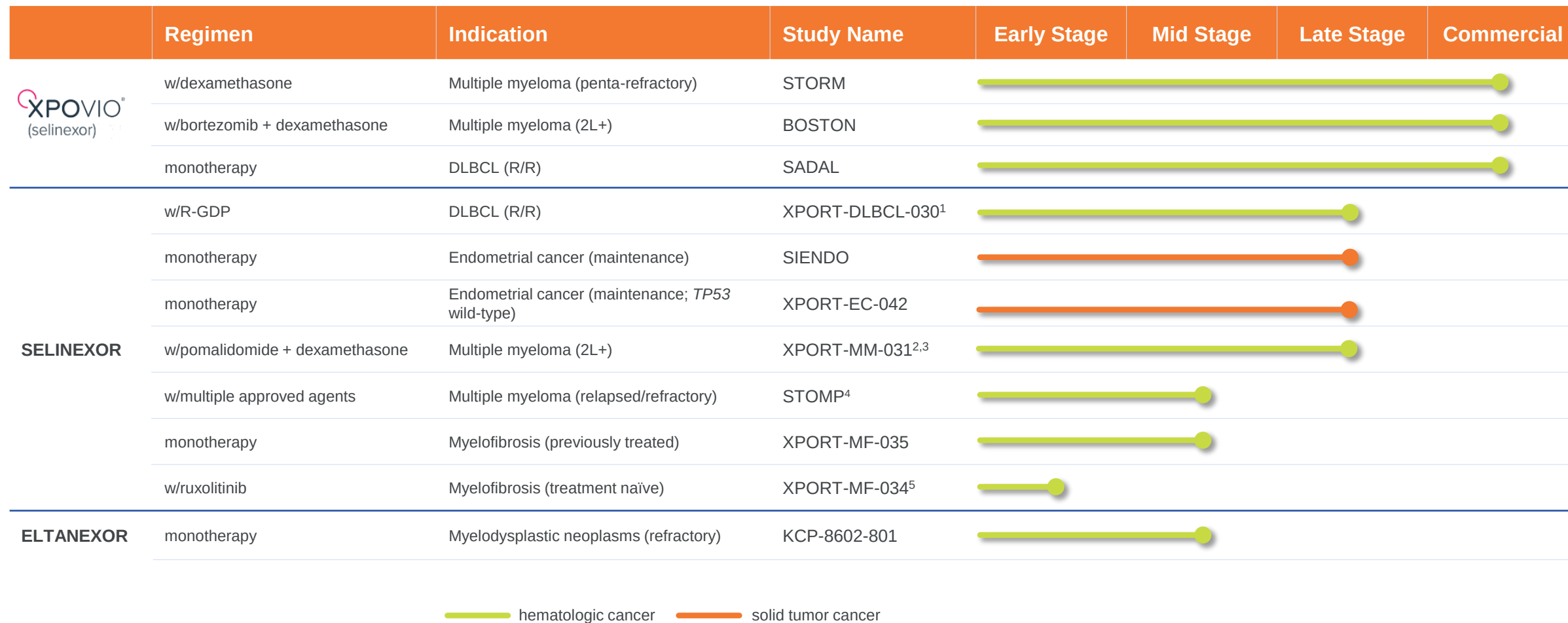
- US product revenue guidance of \$125-\$140M in 2023
- Drive depth within the broad base of XPOVIO prescribers in the Community
- Reinforce the positioning of XPOVIO in the 2-4L, following the anti-CD38 class
- Leverage positive experiences with lower dosage and earlier line utilization of XPOVIO
- Generate further data on the role and effectiveness of XPOVIO pre and post-T cell mediated therapies

Reshma Rangwala, MD, PhD
Chief Medical Officer

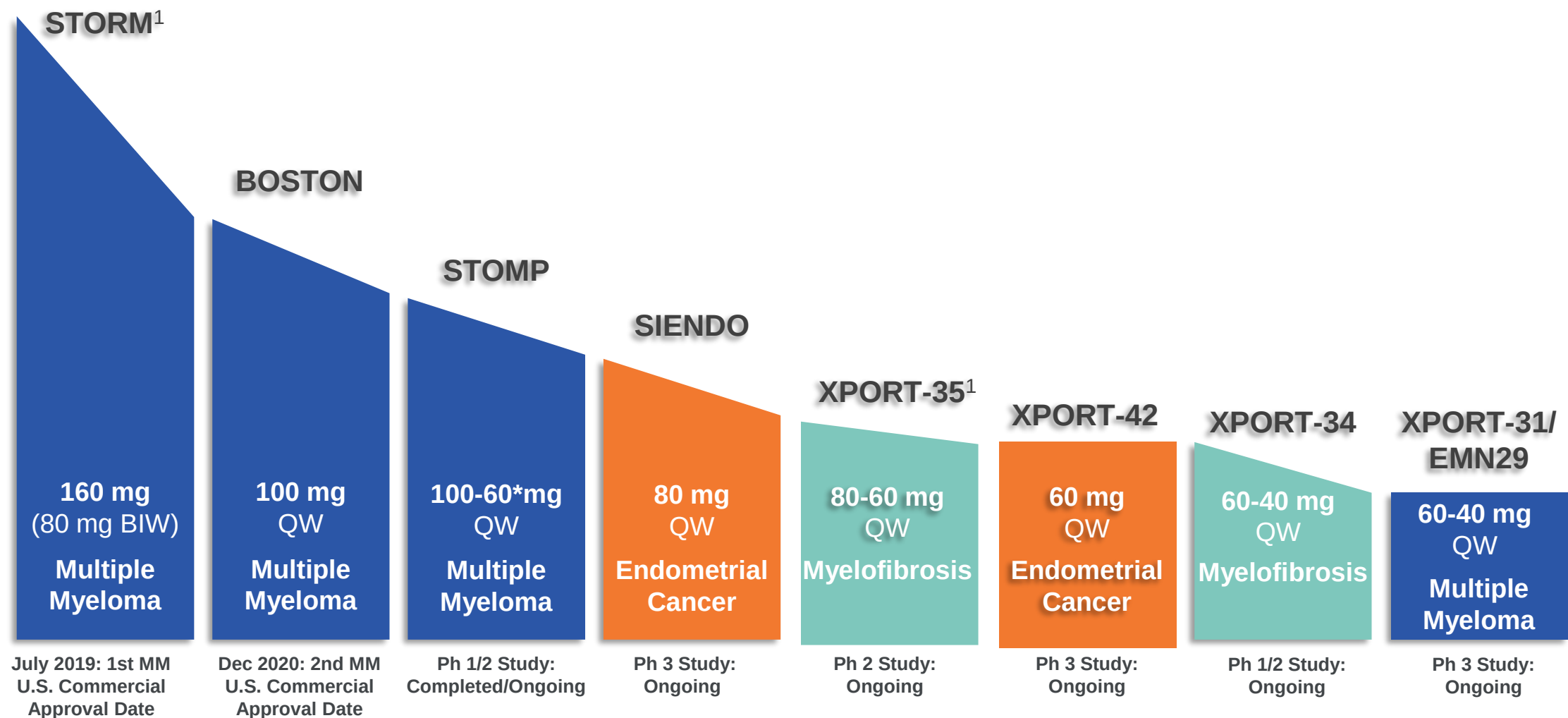
PIPELINE UPDATE



Progressing Focused Pipeline Across Cancers With High Unmet Needs



Optimizing Selinexor Dose to Improve Patient Experience and Overall Benefit



1. Following 80mg weekly * 2 cycles



ENDOMETRIAL CANCER

Potential for Significant Paradigm Shift for the Treatment of Women with Advanced or Recurrent *TP53* Wild-Type Endometrial Cancer

Phase 3 SIENDO study

Generated strong hypothesis in patients with *TP53* wild-type EC

Addressing a significant unmet need

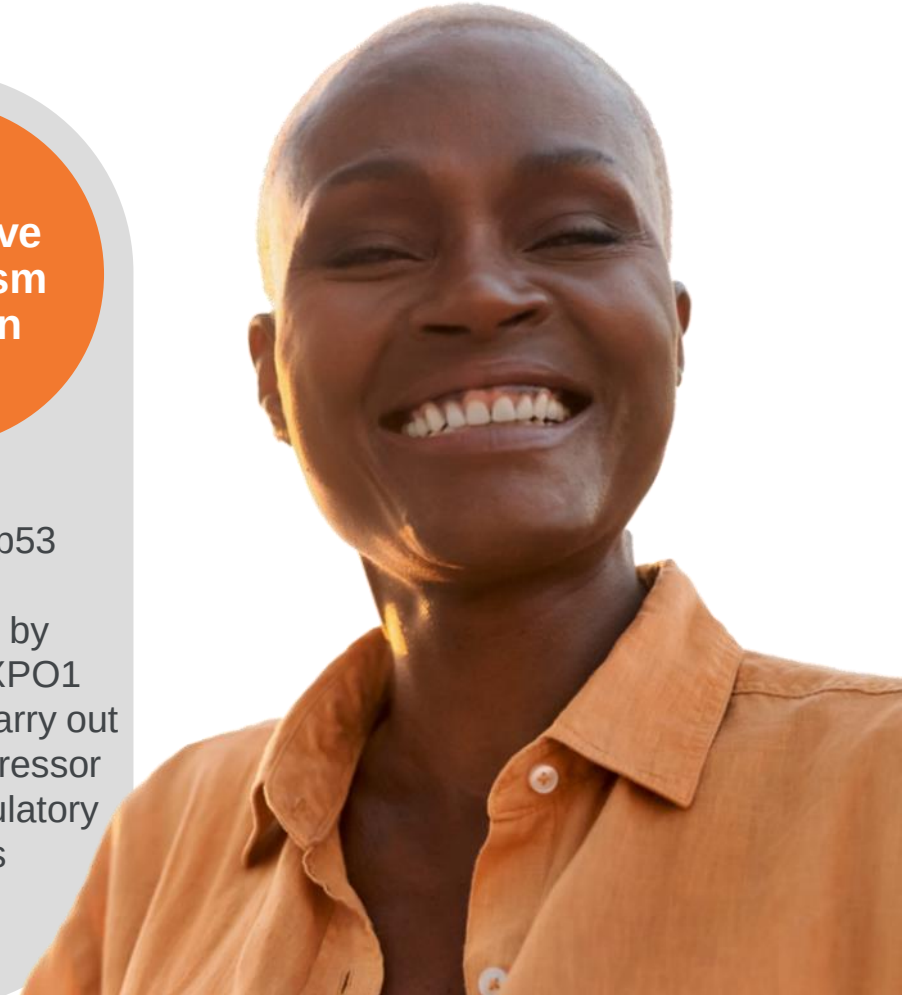
Currently no FDA approved treatments in the maintenance setting

Significant market opportunity

~14K patients diagnosed with advanced and recurrent endometrial cancer in the U.S. each year¹
~50% of these patients have *TP53* wild-type EC²

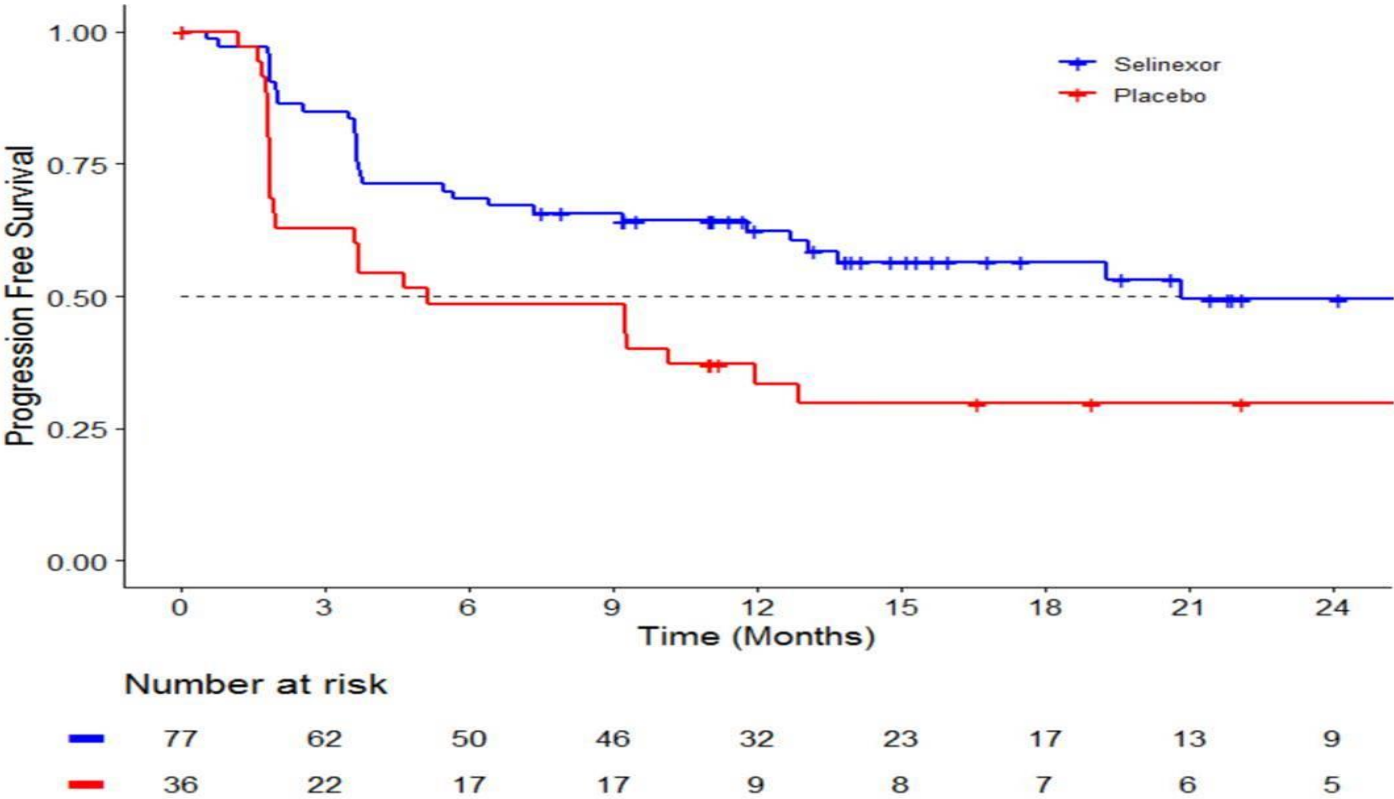
Supportive Mechanism of Action

Forced retention of p53 in the cell nucleus by inhibition of XPO1 allows p53 to carry out its tumor suppressor and other regulatory functions



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.

Updated Exploratory Subgroup Analysis from SIENDO Study in Patients with TP53 Wild Type Endometrial Cancer^{1,2} Further Supports Rationale for Evaluating Selinexor as Maintenance Therapy



Median PFS
Selinexor (n=77): **20.8 months**
Placebo (n=36): **5.2 months**

- Most common adverse events (AE) were nausea, vomiting and diarrhea with no meaningful change in the AE profile since last data cut
- Most common Gr 3/4 AEs were neutropenia (18%), nausea (12%), thrombocytopenia (9%) and fatigue (8%). No Grade 5 events observed
- AEs were generally manageable with supportive care and dose modifications

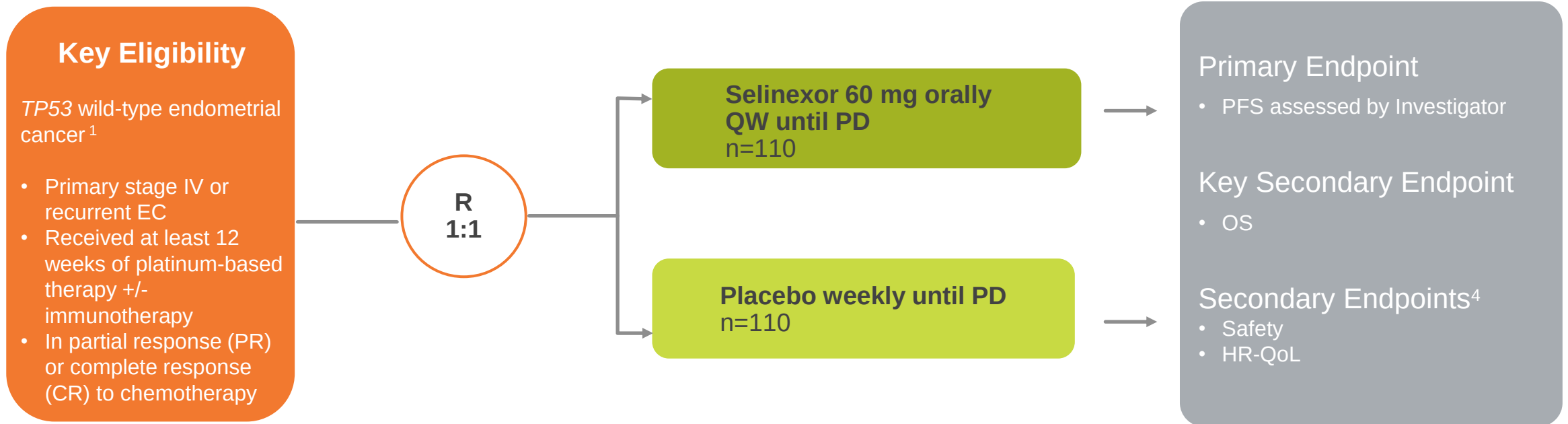
The safety and efficacy of selinexor in endometrial cancer has not been established and has not been approved by the U.S. FDA or any other regulatory authority.

1. TP53 WT/MUT status of patients under continued evaluation. 10% of patients on the selinexor arm and 7% of patients on the control arm have no tumor TP53 status.
2. Preliminary data from pre-specified exploratory subgroup analysis as of the database cut date of November 30, 2022.

Initiated Global Phase 3 Pivotal Study; *TP53* Mutation Status Is Assessed by Companion Diagnostic Partner Foundation Medicine¹

XPORT-EC-042 Global Phase 3, Randomized, Double-Blind, Trial of Selinexor as Maintenance Therapy for Patients with *TP53* Wild-type, Advanced or Recurrent Endometrial Cancer (N=220)

Study in Collaboration with ENGOT² and GOG³



- HR-QoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PD, progressive disease; QW, every week

1. Utilizing Foundation Medicine's tissue-based next generation sequencing test to identify *TP53* status

2. European Network for Gynaecological Oncological Trial groups; 3. Gynecologic Oncology (GOG) Foundation

4. Selected secondary endpoints

MYELOFIBROSIS



Opportunity to Transform 1L Myelofibrosis Treatment with a Combination Approach

Treatment Landscape and Unmet Need

~17,000 living with MF in the U.S. each year¹

Significant unmet need in 1L treatment with current standard of care, ruxolitinib:

- ~40-45% of patients achieve SVR35² and TSS50²
- ~25% of male patients achieve an SVR35 at week 24³
- ~23% patients who start on ruxolitinib 15 mg BID achieve an SVR35 at week 24⁴
 - ~70% patients in the real world start on ruxolitinib 15 mg BID or less⁵

Overall survival is limited; SVR35 may be a potential leading indicator of overall survival⁶

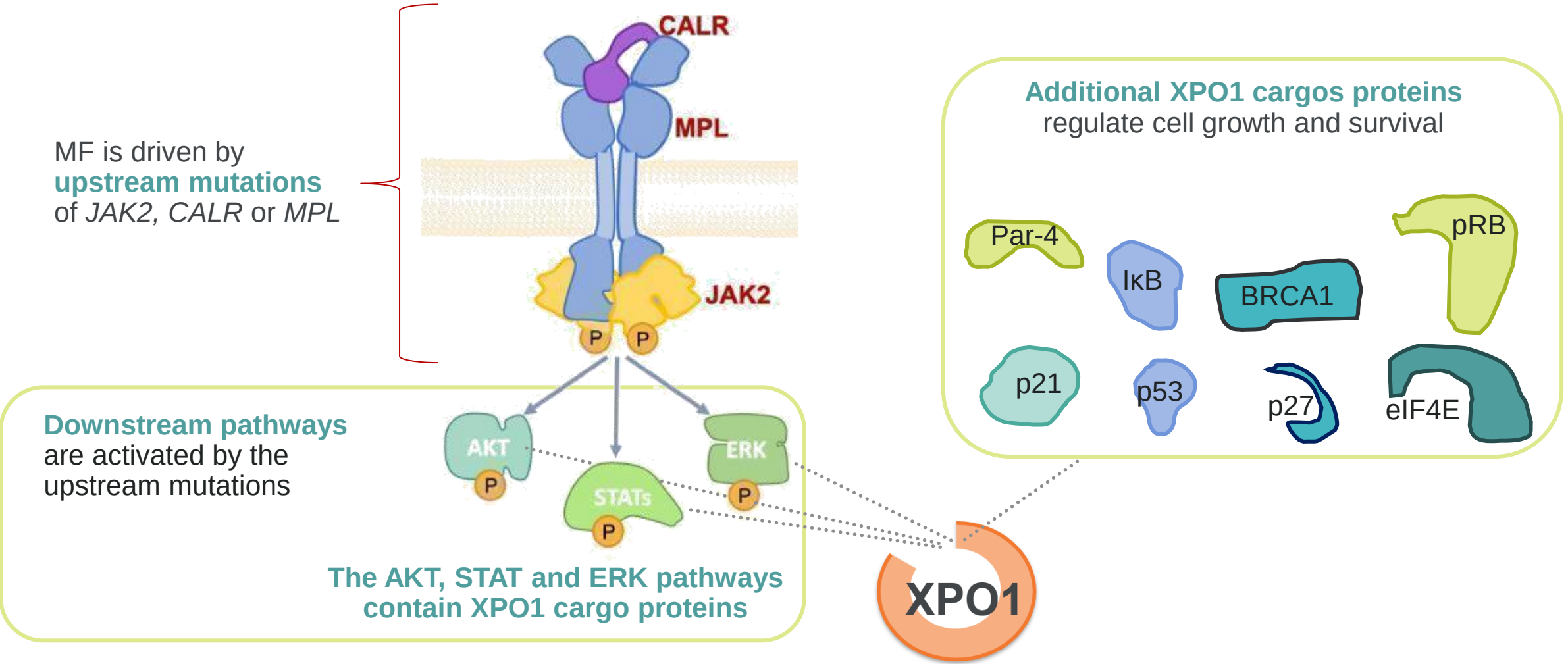
No other approved class of therapies other than JAK inhibitors

Selinexor has the Potential to Substantially Improve Outcomes

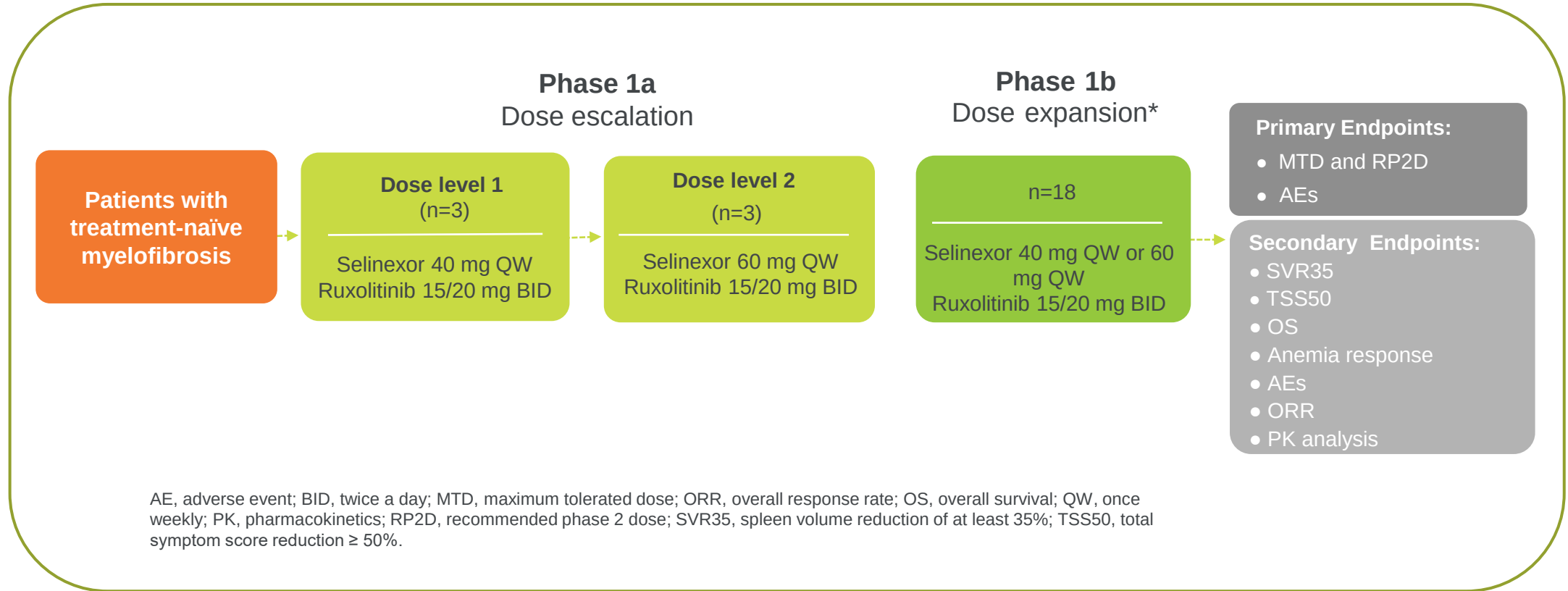
- ✓ XPO1 inhibition as a fundamental mechanism in MF with potential synergism with ruxolitinib
- ✓ Decrease size of spleen
- ✓ Improve constitutional symptoms
- ✓ Improve hemoglobin/anemia
- ✓ Disease modifying
- ✓ Established and manageable safety profile

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.

Selinexor Can Inhibit Multiple Targets of the JAK Pathway, Enabling Independent Suppression of MF cells and Potentially Complementing the Function of JAKi's^{1,2,3,4,5}



Phase 1 Study (XPORT-MF-034¹) Evaluating Selinexor in Combination with Ruxolitinib in Treatment-naïve Myelofibrosis



* Enrollment completed; 24 patients had been assigned to either a 40 mg or 60 mg once weekly dose of selinexor, in combination with ruxolitinib 15/20 mg BID (twice daily)

Encouraging Preliminary Week 24 Data^{1,2} From Evaluable Patients Across Key Efficacy Endpoints from Phase 1 Study (XPORT-MF-034)

SPLEEN RESPONSES (SVR35)

92% of evaluable patients³ (11/12) achieved SVR35 at week 24

100% of evaluable patients³ (12/12) achieved an SVR35 at anytime

REDUCTION IN TOTAL SYMPTOM SCORES (TSS50)

67% of evaluable patients³ (4/6) achieved TSS50 at week 24

POSITIVE IMPACTS ON HEMOGLOBIN LEVELS

57% of patients⁴ (13/23) maintained stable hemoglobin ($\pm$ 2g/dL) or improved hemoglobin level (>2 g/dL increase) at last follow up

SAFETY AND TOLERABILITY

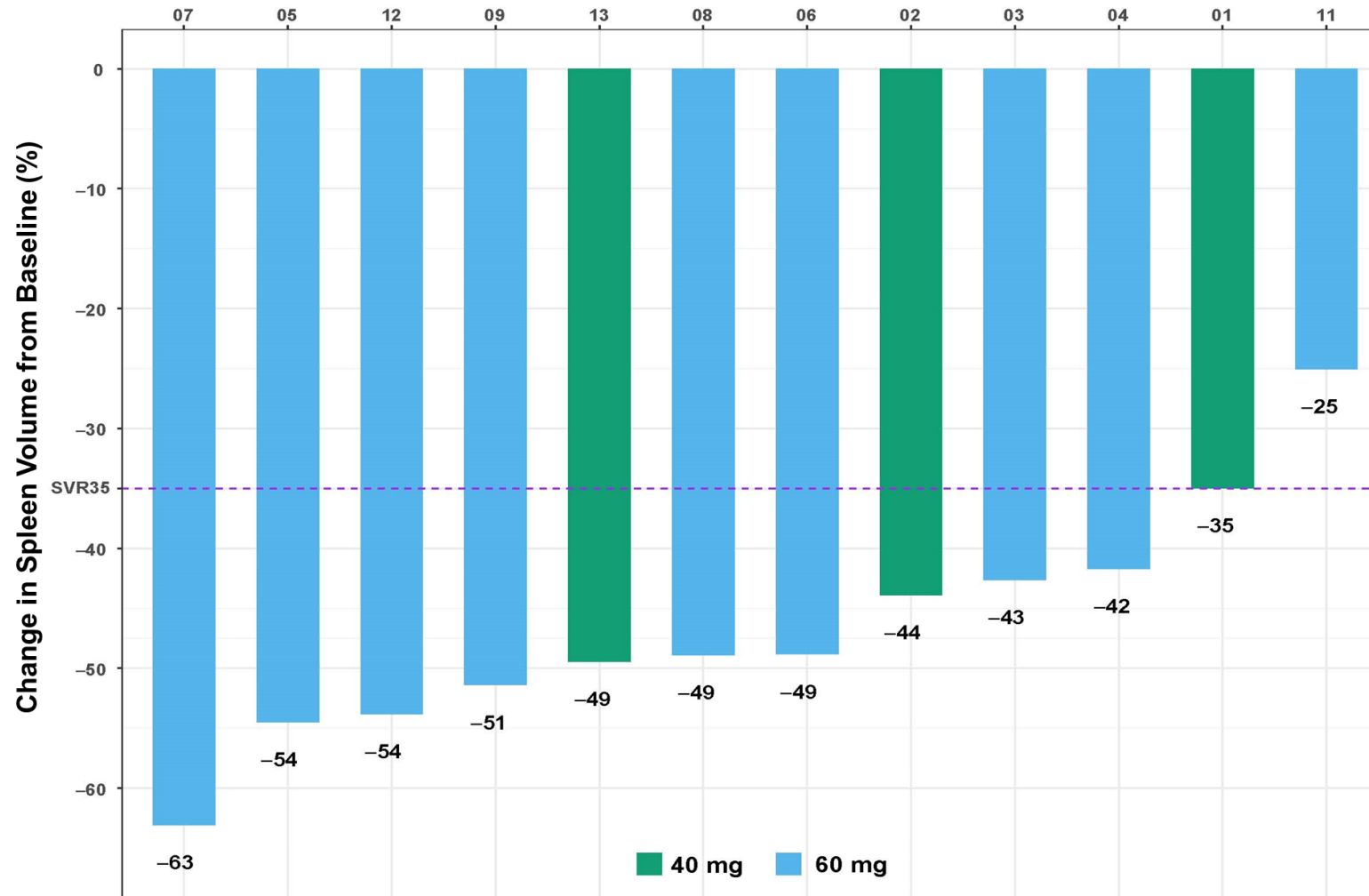
Most common TEAEs⁵ (n=24):
Nausea, anemia and fatigue (majority Grade 1-2)

Most common Grade $\geq$ 3 TEAEs:
Anemia (38%) and thrombocytopenia (21%)

Preliminary TSS50 analysis only includes patients who filled out all their symptom evaluation forms (n=6); other 6 patients who were evaluable for SVR analysis remained on therapy. Based on symptom scores collected from patients' medical charts, an updated TSS50 analysis will be presented at a future medical congress in 1H 2023.

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.

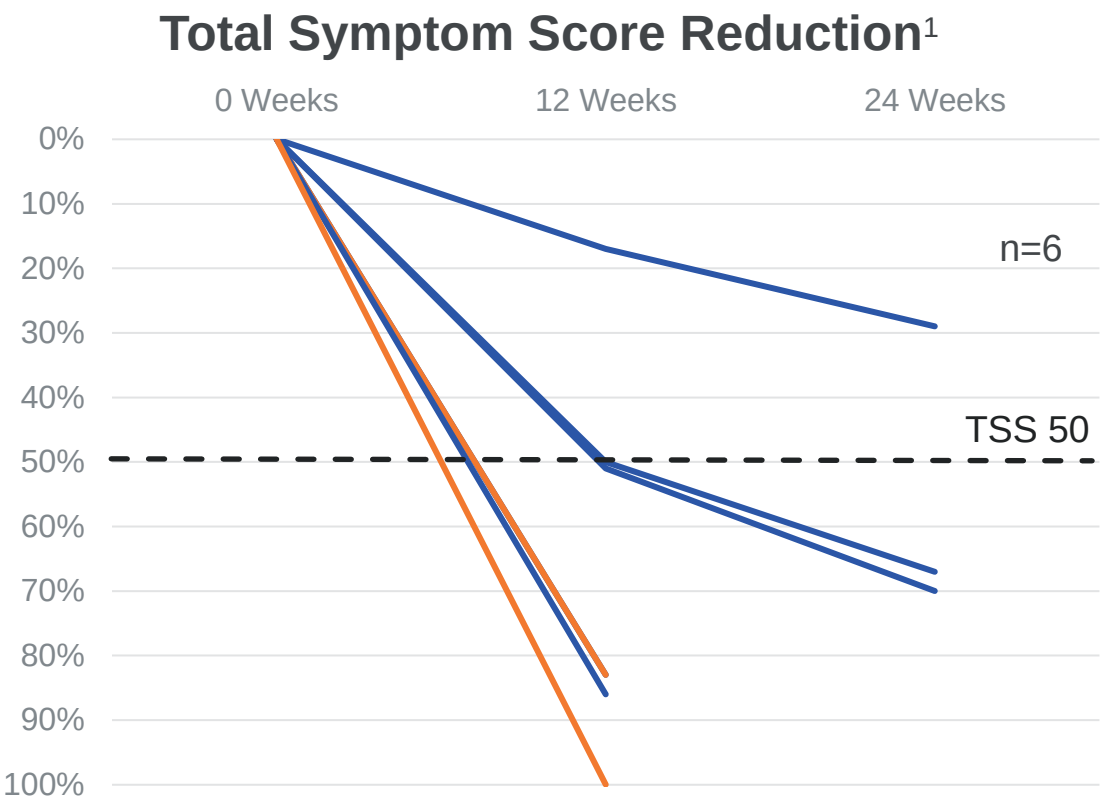
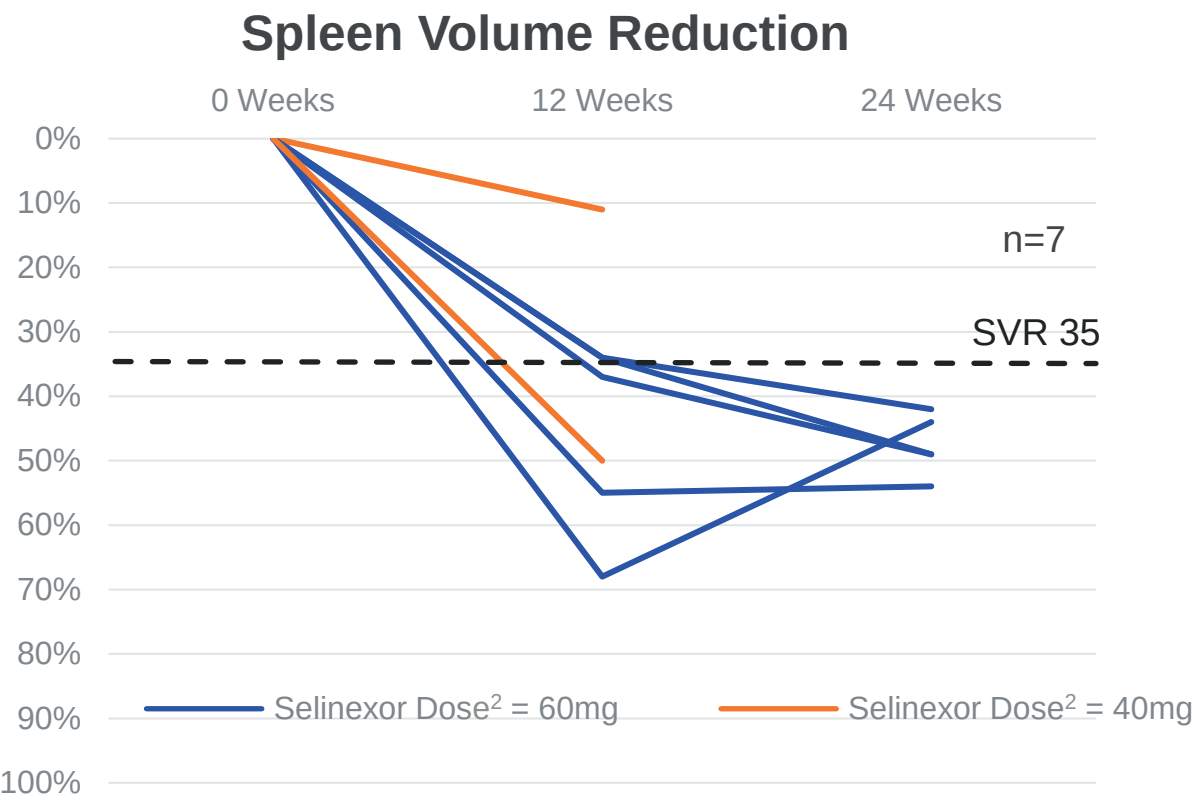
At Week 24, All Evaluable Patients* had Reduction in Spleen Volume Relative to Baseline



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.

Patients Maintained on a Suboptimal Dose of Ruxolitinib 5 mg in Combination with Selinexor Achieved Benefit

Retrospective, Exploratory Analysis from Phase 1 Selinexor+Ruxolitinib Study (034)



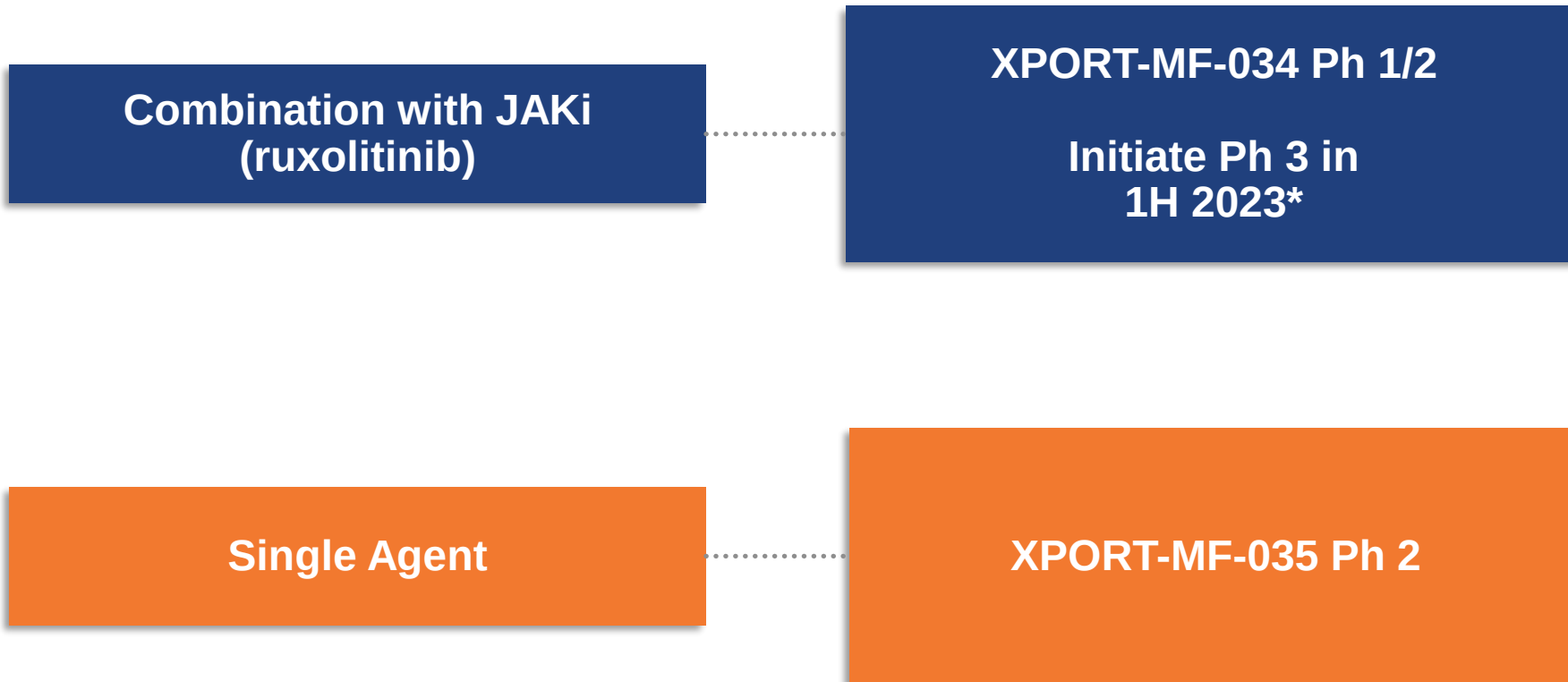
“Based on limited clinical data, long-term maintenance at a 5mg twice daily dose has not shown responses and continued use at this dose should be limited to patients in whom the benefits outweigh the potential risks.” Jakafi (ruxolitinib) U.S. Package Insert, January 2023

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.

1. One patient with missing TSS 50 score
2. Assigned selinexor starting dose

Initial Data Suggest That Selinexor May Have the Greatest Benefit in Treatment-Naïve Myelofibrosis

Evaluating evolving data to determine optimal and efficient developmental pathway that may include monotherapy and innovative combinations



MYELOYDYSPLASTIC NEOPLASMS



Eltanexor Has the Potential to Improve Survival in High Risk Relapsed/Refractory Myelodysplastic Neoplasms

What is Myelodysplastic Neoplasms (MDS)?

- Blood-forming cells in marrow become abnormal and create immature blood cells that are not able to function properly

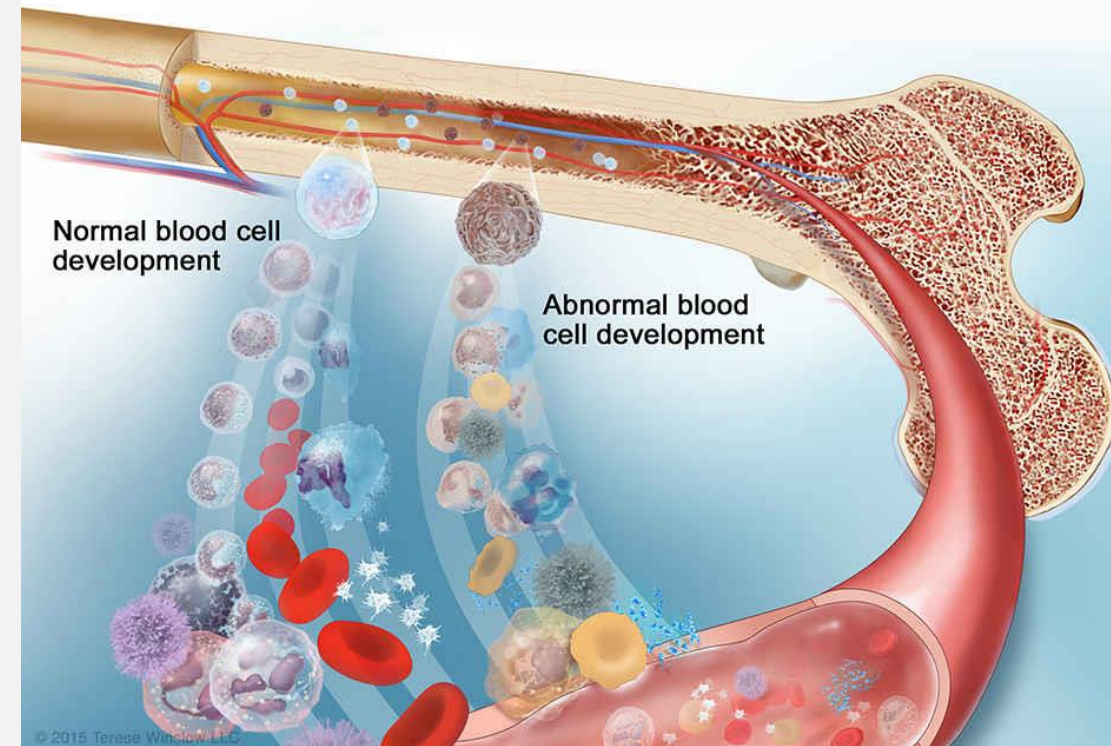
Treatment Landscape

- Hypomethylating agents (HMA) are the current standard of care for patients with newly diagnosed, higher-risk MDS
- Approximately 50% of patients respond; responses typically last <2 years²

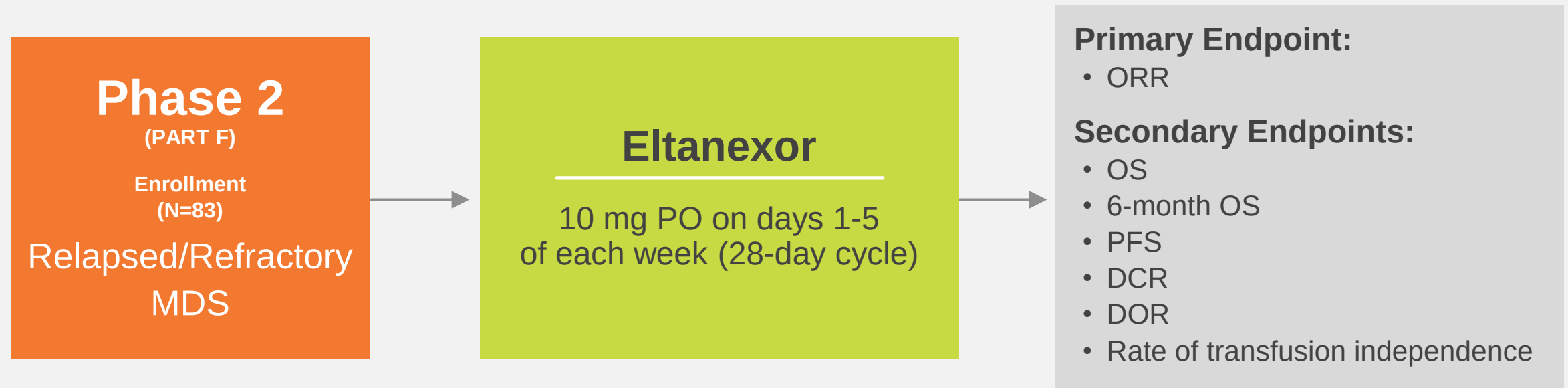
Opportunity and Unmet Need

- Prognosis in relapsed/refractory disease is poor, with an **expected survival of 4-6 months**^{3,4}
- No currently approved therapies for HMA-refractory disease

~15,000 patients diagnosed with intermediate-to-high risk MDS each year in the US¹



Phase 2 Expansion of the Ongoing Phase 1/2 Study of Single-Agent Eltanexor in Relapsed/Refractory MDS



Data from planned interim analysis (n=30) expected in 1H 2023

MICHAEL MASON
Chief Financial Officer

FINANCIAL RESULTS AND GUIDANCE



4Q and FY 2022 Financial Results

Statements of Operations (\$ millions)	4Q 2022	4Q 2021	FY 2022	FY 2021
Total Revenue	\$33.6	\$126.3	\$157.1	\$209.8
XPOVIO Net Sales	31.1	29.8	120.4	98.4
License and Other Revenue	2.5	96.5	36.6	111.4
Total Operating Expenses	\$67.4	\$79.3	\$299.3	\$308.1
Cost of Sales	1.9	0.7	5.2	3.4
Research and Development Expenses	30.9	44.0	148.7	160.8
Selling, General & Administrative Expenses	34.6	34.6	145.4	143.8
Net Income (Loss)	(\$38.5)	\$38.7	(\$165.3)	(\$124.1)
Net Income (Loss) per share	(\$0.43)	\$0.46	(\$2.02)	(\$1.65)

Balance Sheet (\$MM)	Dec 31, 2022	Dec 31, 2021
Cash, Cash Equivalents Restricted Cash and Investments	\$279.7	\$235.6

2023 Financial Guidance

- Total Revenue of \$160-\$175 million
- U.S. XPOVIO Net Product Revenue of \$125-\$140 million
- Non-GAAP R&D and SG&A Expenses of \$260-\$280 million¹
- Cash runway expected to be sufficient to fund planned operations into late 2025

Richard Paulson
Chief Executive Officer

CLOSING REMARKS



Upcoming Milestones for 2023 and Beyond

MULTIPLE MYELOMA

- Leverage commercial capabilities and grow US XPOVIO sales (2023)
- Continuation of global launches (2023)
- Report top-line results from pivotal Phase 3 study evaluating SPd¹ (2H 2024)

ENDOMETRIAL CANCER

- Present updated results from SIENDO study at a medical conference (2023)
- Report top-line results from pivotal Phase 3 study EC-042 in *TP53* wild-type EC (2H 2024)

MYELOFIBROSIS

- Report updated results in Phase 1 trial of selinexor+ ruxolitinib in treatment-naïve MF (1H 2023)
- Initiate pivotal Ph 3 selinexor + ruxolitinib study in treatment-naïve MF (1H 2023)*
- Define optimal mono and innovative combo development plan (1H 2023)

MYELOYDYSPLASTIC NEOPLASMS

- Report interim Phase 2 eltanexor data in relapsed/refractory MDS (1H 2023) and top-line data (2024)



Thank you!
