



Fourth Quarter and Full Year 2023 Financial Results & Business Update

February 29, 2024

On Today's Call

- **Welcome**

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

- **Overview**

Richard Paulson, *President and Chief Executive Officer*

- **Pipeline Update**

Dr. Reshma Rangwala, *Chief Medical Officer*

- **Commercial Highlights**

Sohanya Cheng, *Chief Commercial Officer*

- **Financial Results 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 2024 total revenue, 2024 U.S. net product revenue and 2024 R&D and SG&A expenses; Karyopharm's expected cash runway; beliefs about the market opportunity and annual peak revenue opportunities for selinexor; the ability of selinexor to treat patients with multiple myeloma, endometrial cancer, myelofibrosis, diffuse large B-cell lymphoma, and other diseases; expectations related to future clinical development and potential regulatory submissions of selinexor; expectations with respect to commercialization efforts; submissions to, and the review and potential approval of selinexor 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. 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 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; 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 September 30, 2023, which was filed with the Securities and Exchange Commission (SEC) on November 2, 2023, 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



Driven to Positively Impact Lives and Defeat Cancer Through Scientific Innovation

Committed to Driving Value with Next Stage of Growth

Novel & Differentiated Mechanism of Action

Transformative Late-Stage Clinical Development Opportunities

Strong Financial Position to Deliver 3 Pivotal Studies

Global Commercial Presence & Approvals in over 40 Countries

Potential For ~\$2 Billion Annual Peak U.S. Revenues^{1,2}



Key Program Accomplishments in 2023

Myelofibrosis (MF)

- ❑ Initiated Phase 3 trial of selinexor + ruxolitinib in treatment naïve MF
- ❑ Data presented at ASH 2023 (Phase 1 of selinexor + ruxolitinib in treatment-naïve MF) showed encouraging spleen reduction, symptom improvement, long-term durability and was suggestive of disease modification
- ❑ Received Fast Track Designation from the FDA for selinexor for the treatment of patients with MF

Endometrial Cancer (EC)

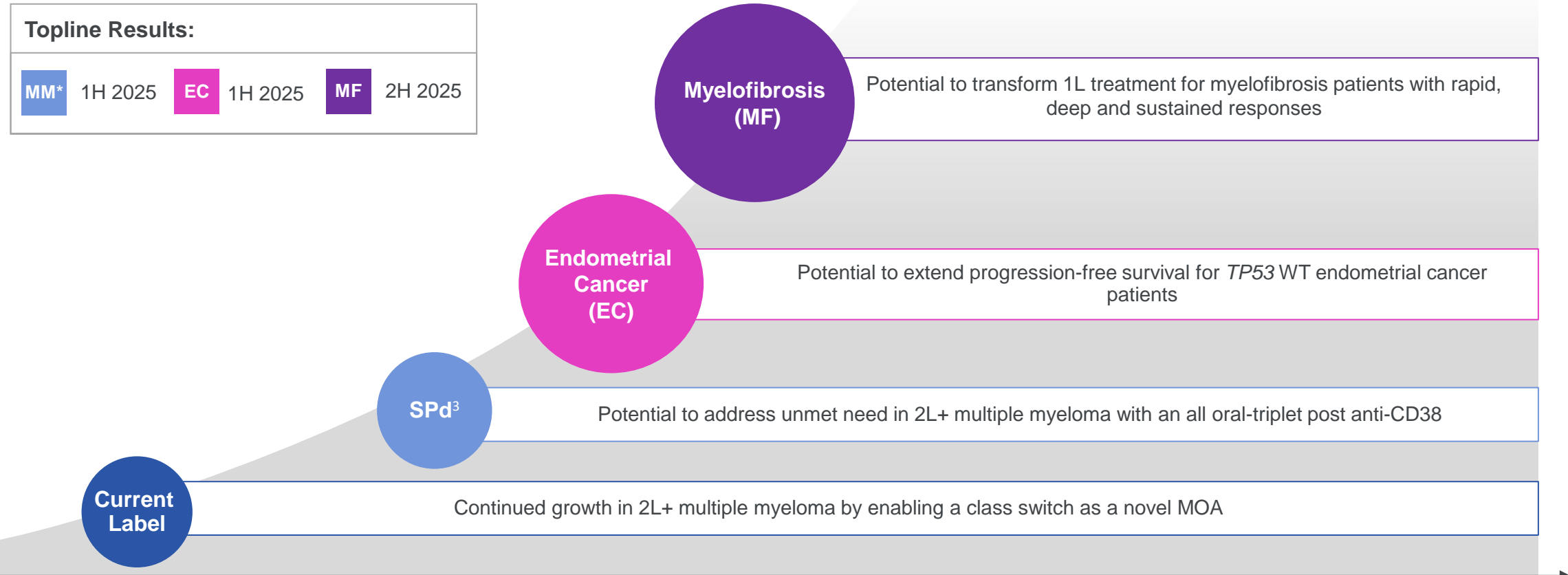
- ❑ Long-term progression free survival (PFS) from the *TP53* wild-type (WT) exploratory subgroup from the Phase 3 SIENDO trial presented at the ASCO Plenary Series showed meaningful PFS benefit
- ❑ Preliminary analysis in the *TP53* wild-type exploratory subgroup from the Phase 3 SIENDO trial, presented as an oral presentation at IGCS 2023, showed encouraging overall survival

Multiple Myeloma (MM)

- ❑ Continued XPOVIO shift to earlier lines, with patient mix ~70% in the 2-4L
- ❑ Update from NCCN guidelines to list XvD¹ as Category 1 & Preferred in lenalidomide-refractory patients
- ❑ Presentation of selinexor (40mg)+Pd^{2,3} showed an optimal risk-benefit profile
- ❑ Further approvals and commercial launches by partners ex-US

Positioned for Success with 3 Pivotal Studies in Indications with Total US Potential of ~\$2B Annual Peak Revenues^{1,2}

Data Readouts from Selinexor Expected in 2025



* Multiple myeloma.
1. Includes projected potential selinexor revenues in: JAKi-naïve myelofibrosis, TP53 wild type endometrial cancer and multiple myeloma.
2. Annual U.S. peak revenue opportunity is not guidance, but instead represents what the company believes to be Karyopharm's peak revenue opportunity based on internal estimates, including market research conducted for each indication.
3. Selinexor + pomalidomide + dexamethasone.

Reshma Rangwala, MD, PhD
Chief Medical Officer

PIPELINE UPDATE



Focused High Potential Pipeline with 3 Pivotal Studies Across Cancers With High Unmet Needs

	Regimen	Indication	Study Name	Early Stage	Mid Stage	Late Stage	Commercial
XPOVIO® (selinexor)	w/dexamethasone	Multiple myeloma (penta-refractory)	STORM	—————●			
	w/bortezomib + dexamethasone	Multiple myeloma (2L+)	BOSTON	—————●			
	monotherapy	DLBCL (R/R)	SADAL	—————●			
SELINEXOR Pivotal Phase 3s	w/pomalidomide + dexamethasone	Multiple myeloma (2L+; post-anti CD38)	XPORT-MM-031 ^{1,2}	—————●			
	w/ruxolitinib	Myelofibrosis (treatment naïve)	XPORT-MF-034	—————●			
	monotherapy	Endometrial cancer (maintenance; TP53 wild-type)	XPORT-EC-042	—————●			
SELINEXOR New Studies	Monotherapy ^{3,4} (agreement with SOBI ⁵)	Myelofibrosis (treatment naïve)	XPORT-MF-044	—————●			
	w/mezigdomide ⁶ (agreement with BMS)	Multiple myeloma (relapsed/refractory)	STOMP ⁶	—————●			
	monotherapy	Endometrial cancer (maintenance)	SIENDO	—————●			
	w/R-GDP	DLBCL (R/R)	XPORT-DLBCL-030 ⁷	—————●			
ELTANEXOR	monotherapy	Myelodysplastic neoplasms (relapsed/refractory)	KPT-8602-801	—————●			

—————● hematologic cancer
 —————● solid tumor cancer

MYELOFIBROSIS



Selinexor Has the Potential to Define a New Treatment Paradigm in MF¹

Treatment Landscape and Unmet Need

Population living with MF:

- ~20,000 in the U.S²; ~17,000 in EU²

No other approved class of therapy other than JAK inhibitors

- Ruxolitinib generates over \$1 billion³ revenues annually in MF in the U.S.

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

- Only ~35% of patients achieve SVR35 with ruxolitinib⁴
- <50% achieve TSS50⁴

Selinexor

- ✓ XPO1 inhibition is a novel and potentially fundamental mechanism in MF
- ✓ Synergism with ruxolitinib observed in preclinical data⁵
- ✓ Rapid, deep and sustained spleen response, robust symptom improvement and rapid, sustained cytokine reduction across all subgroups¹
- ✓ Potentially disease modifying with rapid normalization of platelets, maintenance of hemoglobin levels and rapid cytokine reduction
- ✓ Generally tolerable and manageable side effect profile enabling sustained therapy

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. Based on selinexor+ruxolitinib Ph 1 results using data cut as of August 1, 2023

2. Mehta et.al. Leuk Lymphoma 2014 Mar ;55(3):595-600 and US Census data; Clarivate/DRG Epidemiology Data (2022 figures, pub 2019)

3. Incyte Q4 2023 Results

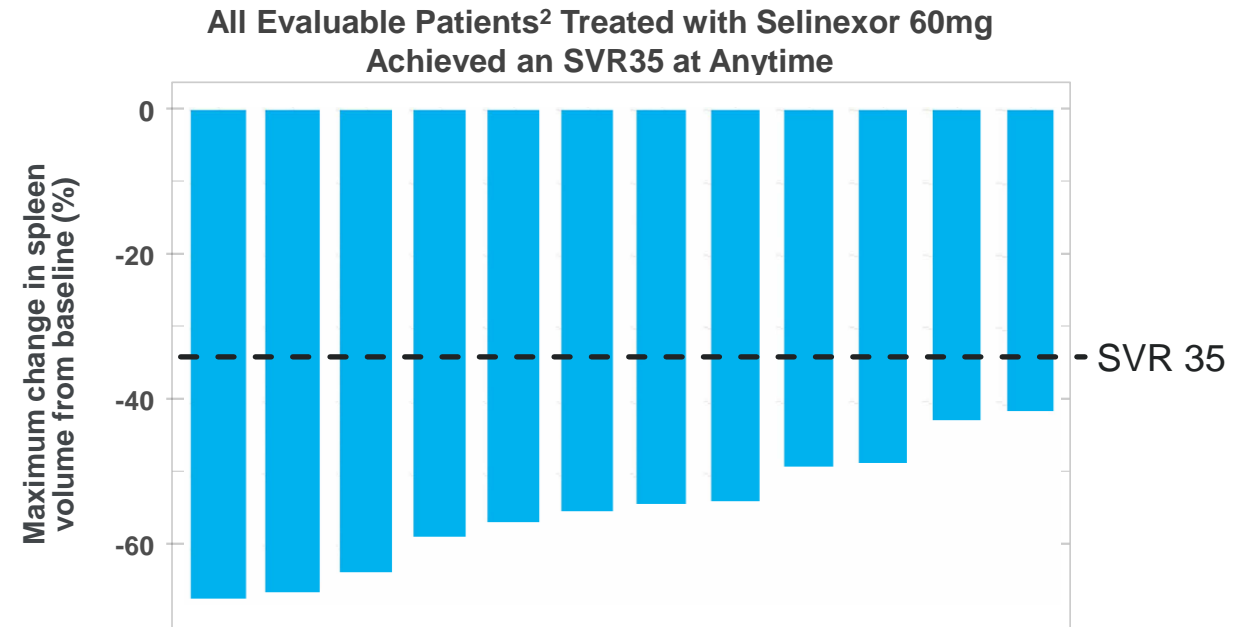
4. MANIFEST and TRANSFORM Phase 3 studies, ASH 2023

5. Al-Ali, et al. Hematologica. 2016;101(9):1065

Rapid and Deep SVR35 Achieved with Selinexor 60mg + Ruxolitinib in Phase 1 Study

		SVR35
		Selinexor 60mg + ruxolitinib
Population	Timepoint	n/N (%)
Efficacy Evaluable	Week 12	10/12 ¹ (83.3)
	Week 24	11/12 (91.7)
Intent-to-Treat	Week 12	10/14 (71.4)
	Week 24	11/14 (78.6)

SVR35, spleen reduction volume $\geq 35\%$



The most common adverse events were GI side effects:

- Nausea (79%, grade ≥ 3 : 7%), anemia (64%, grade ≥ 3 : 43%), thrombocytopenia (64%, grade ≥ 3 : 29%), and fatigue (57%, grade ≥ 3 : 0%)

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Data cut August 1, 2023

Meaningful Improvement Observed in TSS50 and Absolute TSS with Selinexor 60mg + Ruxolitinib at Week 24

		TSS50 ¹
Population	Timepoint	Selinexor 60mg +ruxolitinib n/N (%)
Efficacy Evaluable	Week 12	8/10 ³ (80.0)
	Week 24	7/9⁴ (77.8)
Intent-to-Treat	Week 12	8/12 (66.7)
	Week 24	7/12 (58.3)

		Absolute TSS ²
Timepoint		Selinexor 60mg +ruxolitinib mean (SD*)
Baseline		27.3 (17.43)
Week 24		-18.5 (13.48)

* standard deviation

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.

Data cut August 1, 2023

1. Proportion of patients with ≥50% reduction in TSS from baseline to Week 24 based on modified MPN-SAF TSS V.4.0

2. 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

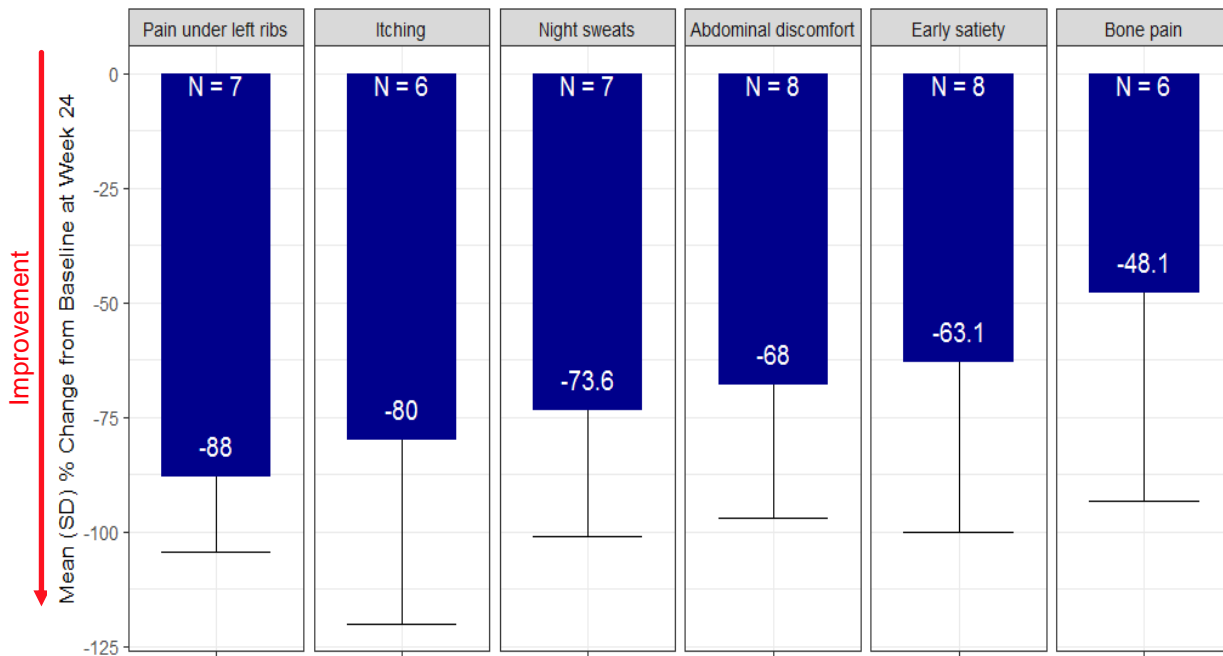
3. One patient discontinued prior to week 12; one patient with missing data at week 12, who subsequently discontinued prior to week 24

4. Two patients discontinued prior to Week 24 and one had missing data

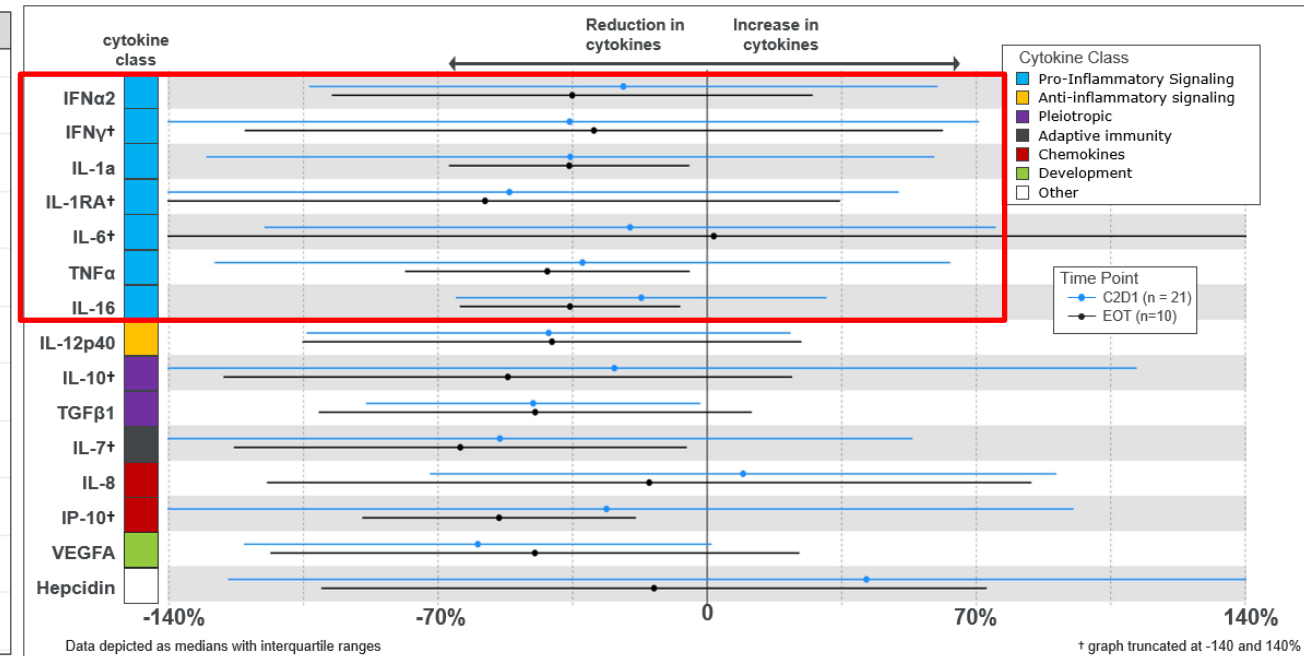
Robust Symptom Improvement Observed with Selinexor + Ruxolitinib

Corroborated by Rapid and Sustained Reduction in Pro-Inflammatory Cytokines and Improvement in all Relevant Symptom Domains

Mean % Change at Week 24 in Symptom Domains¹



Plasma Change in Cytokines²

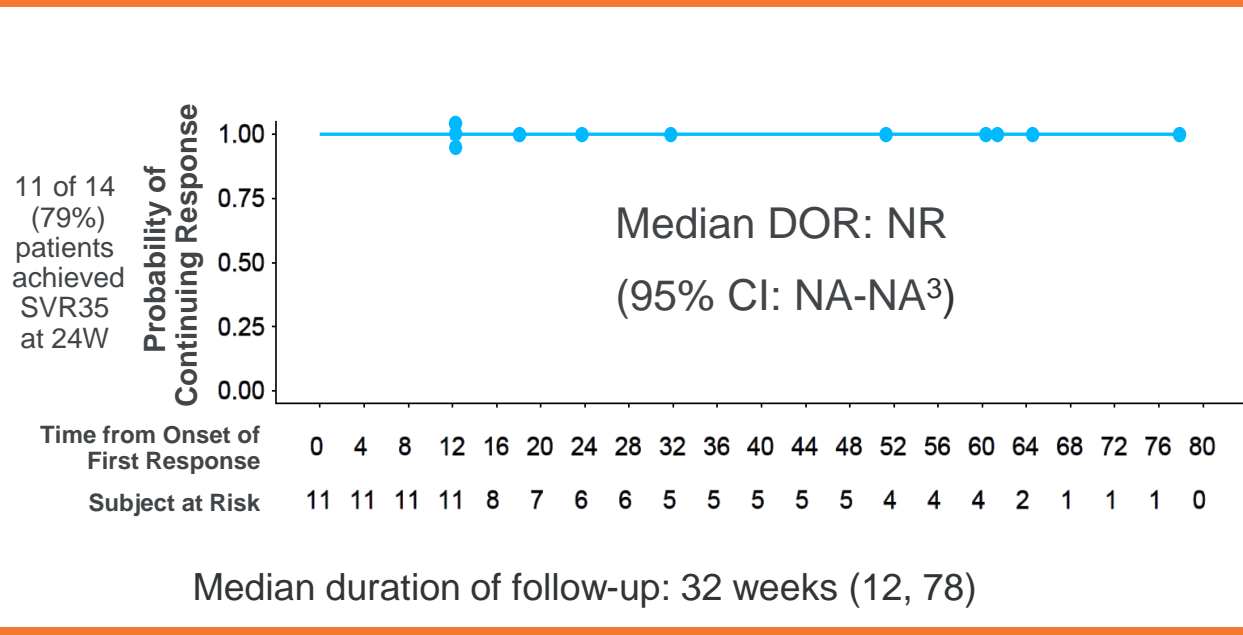


C2D1: Week 4 (blue) ; EOT: End of treatment (black)

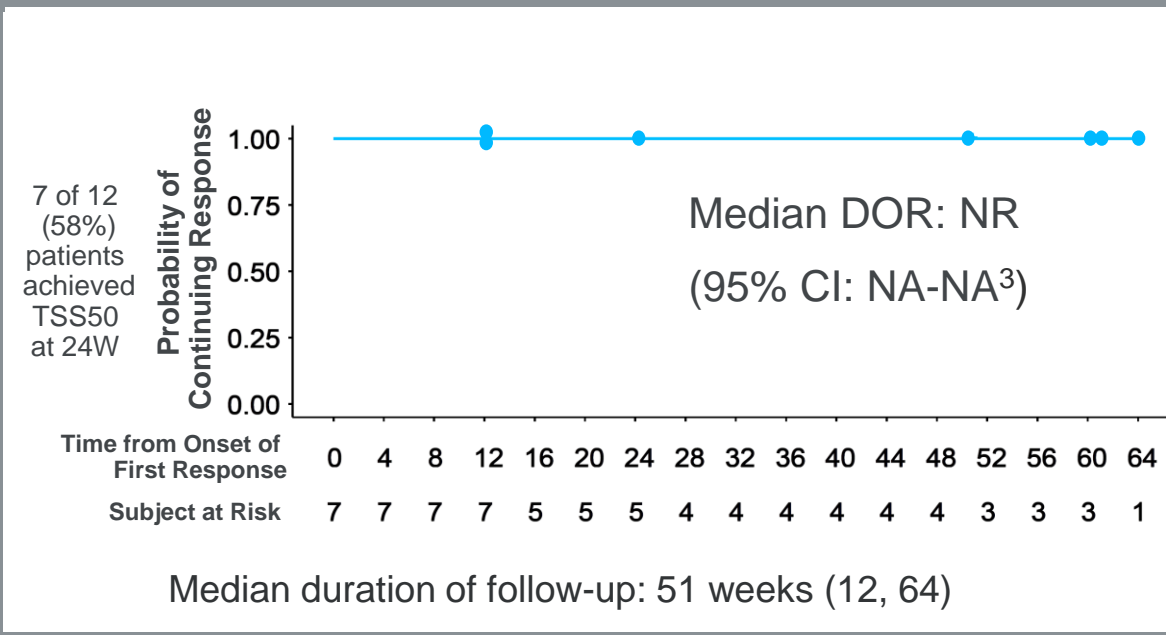
1. Percentage change from baseline to Week 24 was calculated for each symptom domain for subjects (N) who have non-zero and non-missing baseline score and non-missing Week 24 score at the domain. The Bar graph summarizes the mean and SD of the percentage changes.
 2. Plasma sample cytokine levels were assessed by Eve Technologies (Calgary, Alberta, Canada) using the 71-plex, TFGβ, and Hcpidin assays. For patients with available longitudinal samples, screening samples were used to determine % change at C2D1 or EOT. Graph depicts median and interquartile ranges for selected cytokines important for myelofibrosis pathobiology

No Progression for SVR35 or TSS50 Responders^{1,2} on Selinexor 60mg + Ruxolitinib at Data Cutoff of August 1, 2023

SVR35: Selinexor + Ruxolitinib Treatment Shows 100%¹ Probability of Continuing Response



TSS50: Selinexor + Ruxolitinib Treatment Shows 100%² Probability of Continuing Response



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.

Data cut August 1, 2023

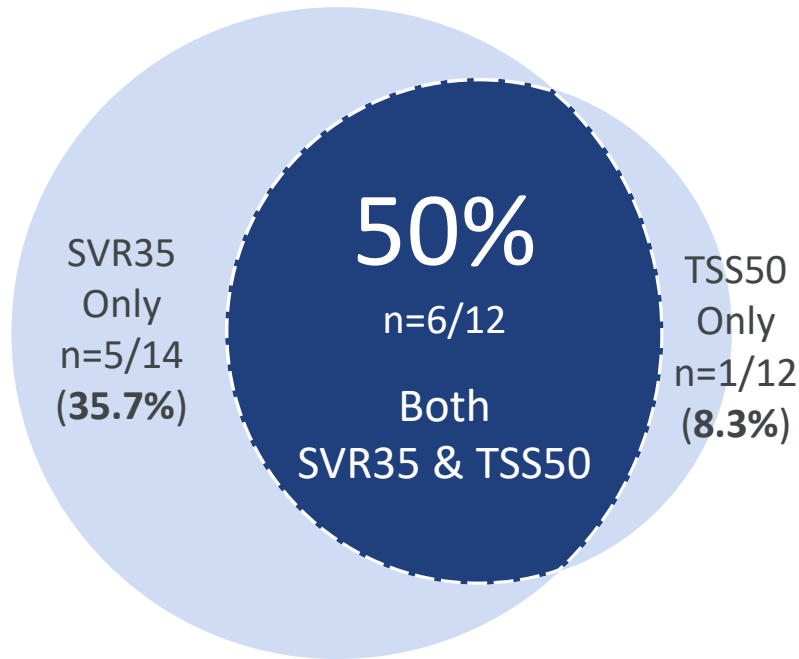
1. SVR progression defined as less than or equal to 35% spleen volume reduction from baseline and more than 25% increase in spleen volume from nadir, assessed radiographically.

2. TSS progression defined as a total symptom score that is equal to or exceeds the baseline value.

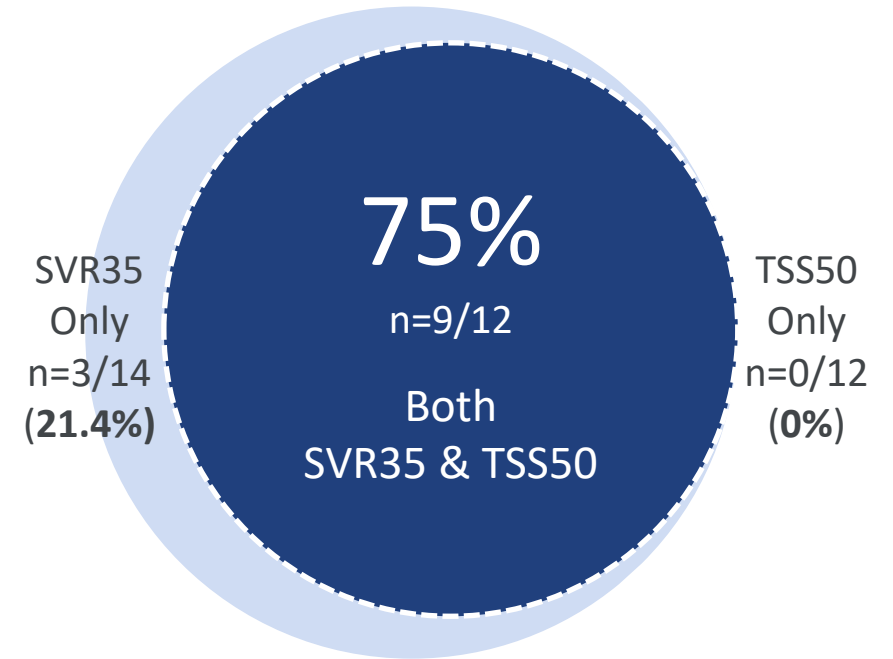
3. Not Applicable.

50% of All Patients Treated with Selinexor 60 mg + Ruxolitinib Achieved SVR35 and TSS50 at Week 24; 75% of Patients Achieved Both at Anytime

Response at Week 24



Response at Anytime

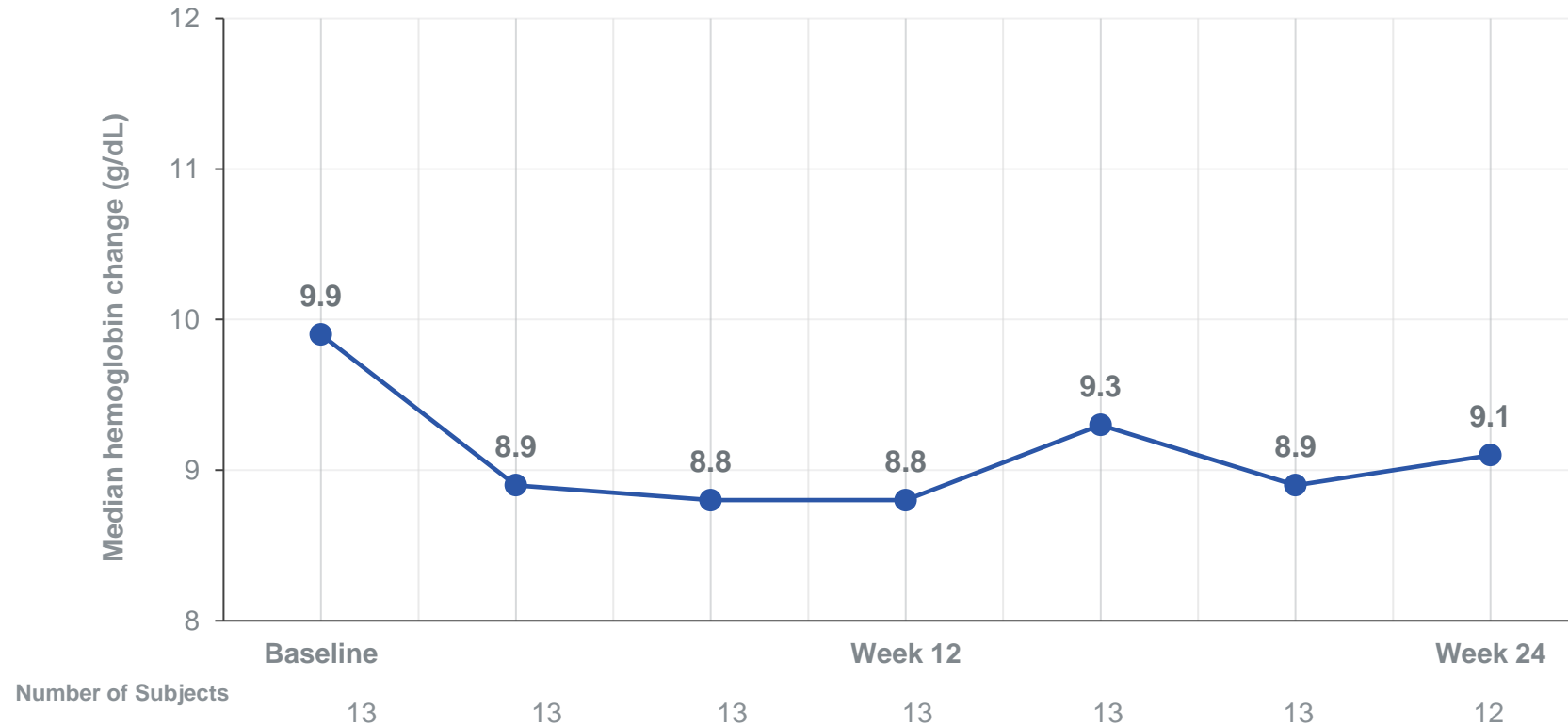


* 2 patients with no baseline symptoms (TSS = 0) were excluded from the TSS50 response and the SVR35/TSS50 dual response analyses.

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.

Markers of Disease Modification Observed With Stable Hemoglobin

Stable Hemoglobin Achieved with Selinexor 60mg QW



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.

Selinexor Plus Ruxolitinib Combination Has The Potential to Significantly Improve SVR and TSS for Myelofibrosis Patients



JOHN MASCARENHAS, MD

Professor of Medicine at the Icahn School of Medicine at Mount Sinai, Director of the Center of Excellence for Blood Cancers and Myeloid Disorders

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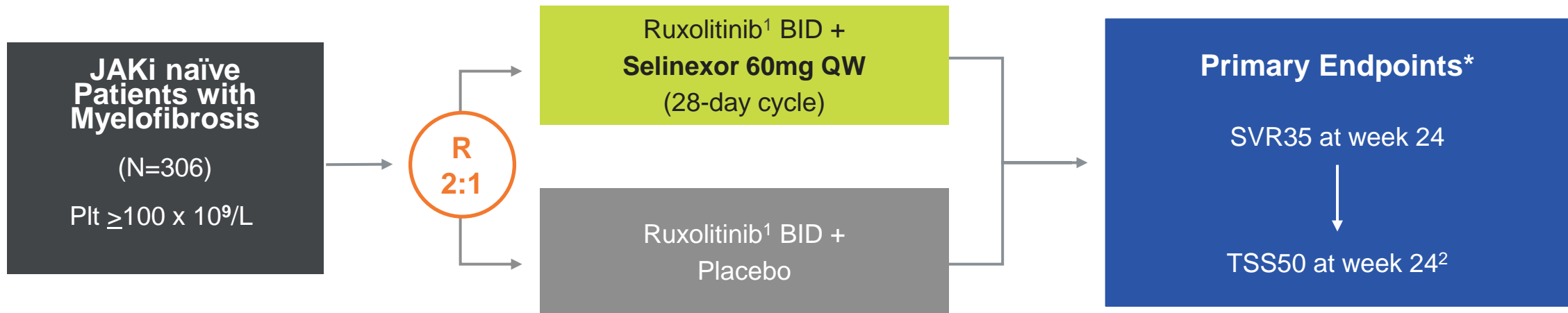
In the Phase 1 study, selinexor 60mg plus ruxolitinib in patients with JAKi naïve myelofibrosis has demonstrated compelling results, particularly regarding spleen and symptom improvement, and illustrates the promising activity of this rational combination regimen in the form of deep and durable responses.

These data suggest that this tolerable and unique combination of XPO1 and JAK inhibition can significantly improve these efficacy measures for first-line myelofibrosis patients.

”

Phase 3 Part of Study (XPORT-MF-034*) Evaluating Selinexor in Combination with Ruxolitinib in Treatment-naïve Myelofibrosis

Study is Actively Enrolling



*NCT04562389

Randomization stratified by:

- Dynamic International Prognostic Scoring System (DIPSS) risk category intermediate -1 vs. intermediate -2 or high-risk
- Spleen volume <1800 cm³ vs. ≥1800 cm³ by MRI/CT scan
- Baseline platelet counts 100-200 x 10⁹/L vs. >200 x 10⁹/L

Top-line Data Expected in 2H 2025



ENDOMETRIAL CANCER

Potential for Significant Paradigm Shift for the Treatment of Women with Advanced or Recurrent *TP53* Wild-Type (WT) EC

Phase 3 SIENDO Study

Generated strong hypothesis in patients with *TP53* WT EC

Targeted Mechanism and Oral Treatment

XPO1 inhibition forces retention of p53 in the cell nucleus, allowing it to carry out its tumor suppressor and other regulatory functions

Addressing a Significant Unmet Need

No FDA approved treatments for pMMR¹ (proficient mismatch repair), which represents ~80% of advanced and recurrent EC²

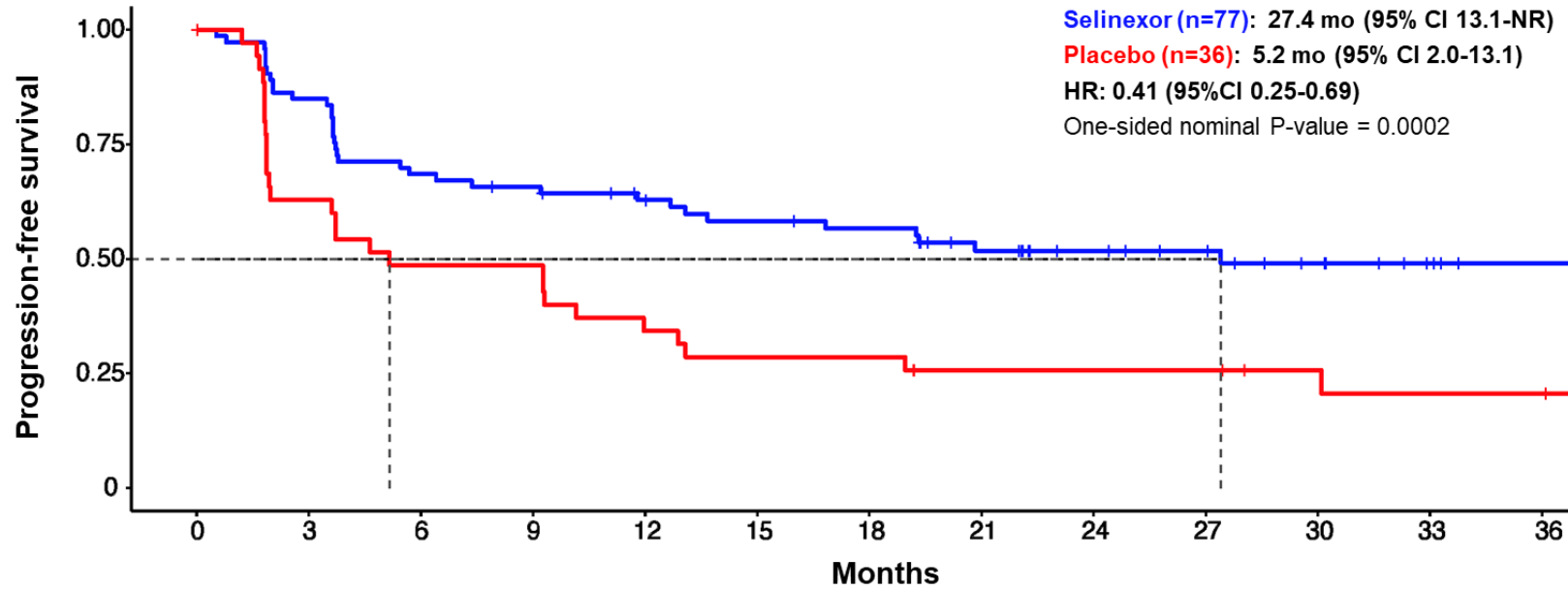
Significant Market Opportunity

~16K patients diagnosed with advanced and recurrent EC in the U.S. each year³
~ >50% have *TP53* WT EC, and 40-55% are *TP53*WT and pMMR^{2,4}



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.

Updated Data from SIENDO Study¹ Indicate Encouraging Signal of PFS Benefit with Median PFS Benefit > Two Years in TP53 Wild Type EC



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Selinexor	77	62	50	47	42	38	36	29	23	20	15	10	7
Placebo	36	22	17	17	12	10	10	7	7	7	5	4	4

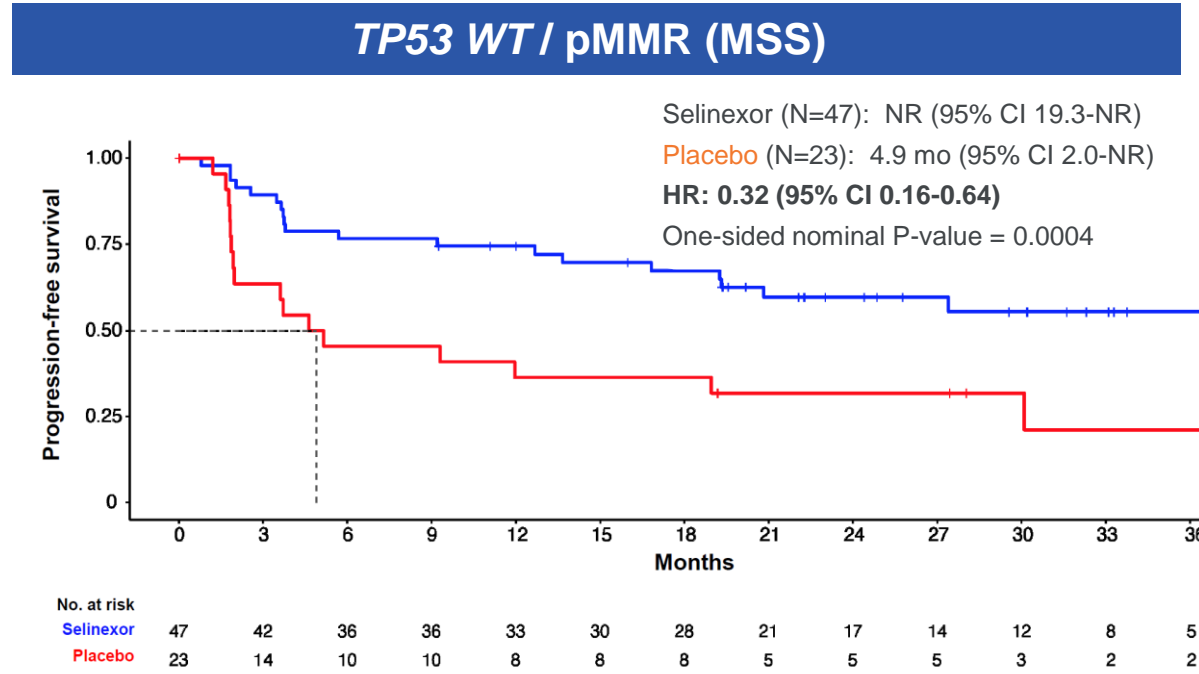
Most common adverse events in TP53 wt exploratory subgroup: Nausea (90%, grade ≥3 : 12%), vomiting (60%, grade ≥3: 3%), thrombocytopenia (42%, grade ≥3 : 10%) and diarrhea (42%, grade ≥3 : 4%). TEAE's leading to discontinuation 16% and death 0%.

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.

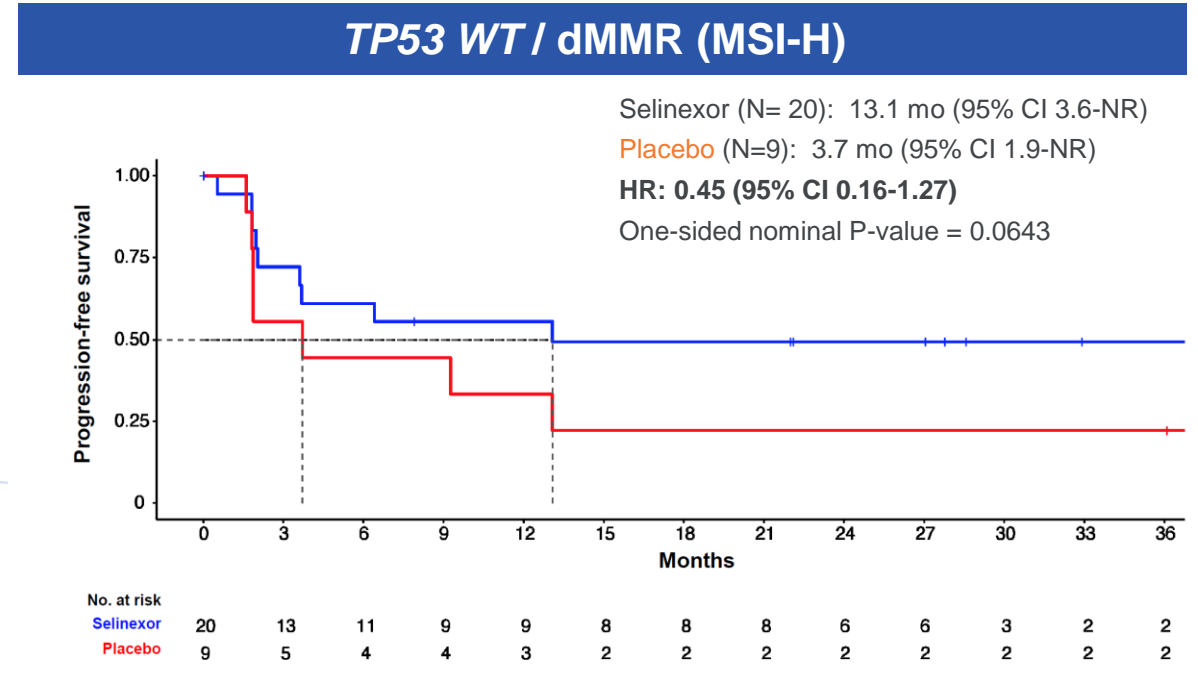
Data cut September 1, 2023

SIENDO Study: Strongest Signal in *TP53* WT pMMR with Median PFS Not Reached; PFS Improvement Observed Regardless of MMR Status

Long Term Follow-Up¹: PFS in *TP53* WT Exploratory Subgroup Based on MMR status



Median follow-up: 31.6 months



Median follow-up: 27.3 months

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.

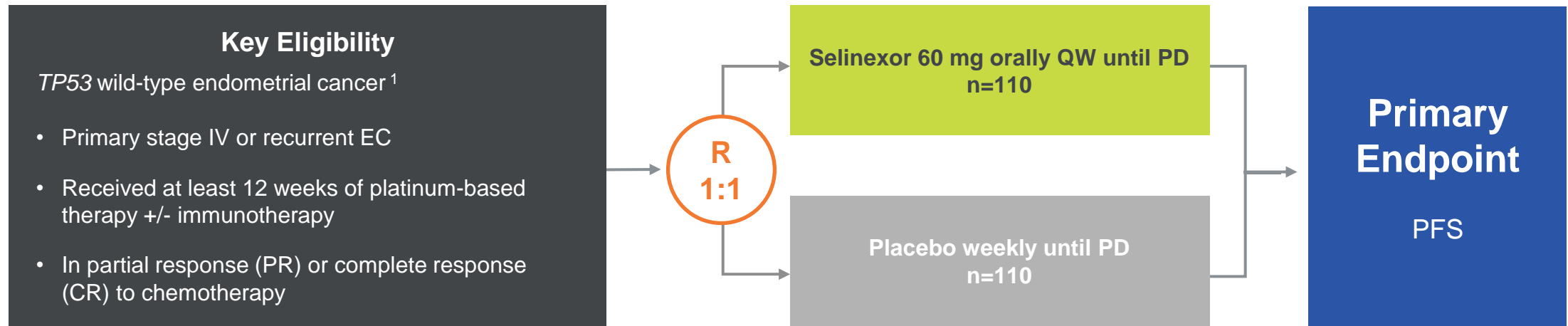
Data cut September 1, 2023

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

Study is Actively Enrolling

TP53 Wild-type Status is Assessed by Companion Diagnostic Partner Foundation Medicine¹

Study in Collaboration with ENGOT² and GOG³



*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.

Top-line Data in 1H 2025

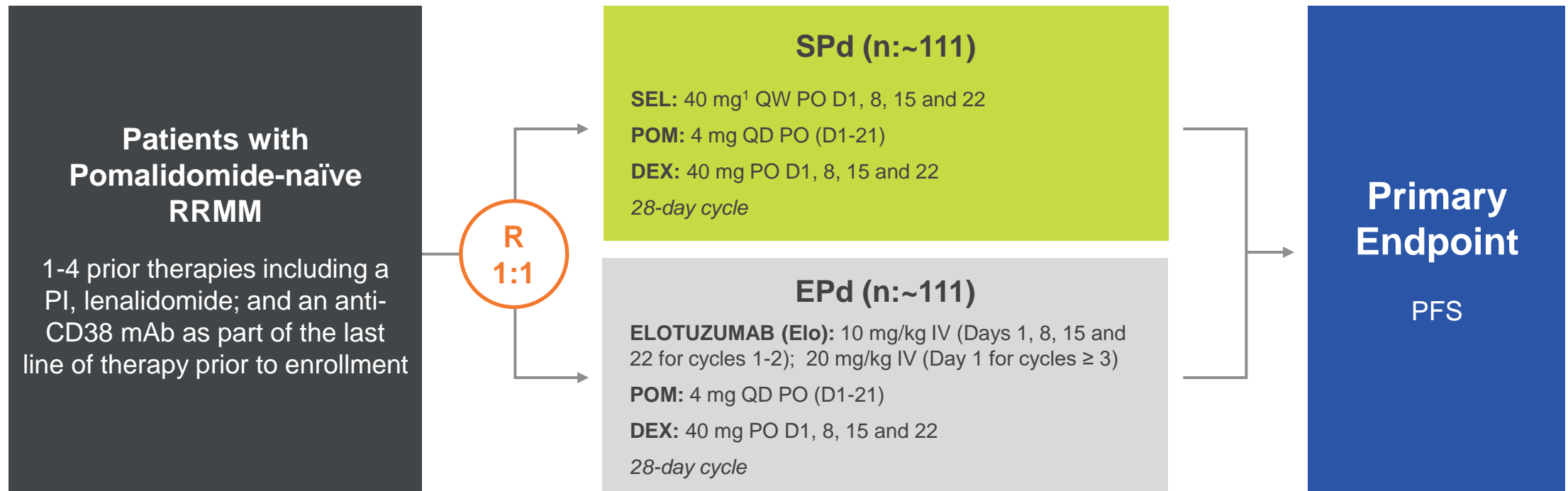
PFS, progression-free survival; PD, progressive disease; QW, every week

MULTIPLE MYELOMA



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

Study is Actively Enrolling



*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 in 1H 2025

PI: proteasome inhibitor; mAb: monoclonal antibody

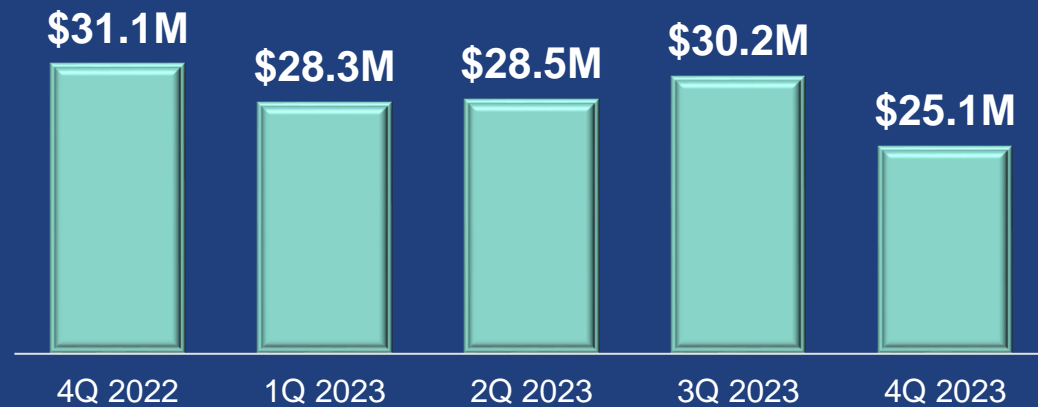
Sohanya Cheng
Chief Commercial Officer

COMMERCIAL HIGHLIGHTS



XPOVIO Update: 4Q 2023 and FY 2023

Net Product Revenue in 2023 Adversely Impacted by Increase in PAP¹, Higher Gross-To-Net and Increased Competition



4Q and FY 2023 Highlights

- XPOVIO Net Product Revenue of \$112M and \$25M for FY 2023 and Q4 2023, respectively
- Demand² growth in the community setting in FY 2023 vs 2022, accounting for ~ two thirds of XPOVIO net product revenue
- Demand² adversely impacted in the academic setting due to increasing competition in 4L+
- ~\$6M impact from PAP due to closure of multiple myeloma foundations. In 2024, fewer patients expected to utilize PAP for co-pay assistance due to re-design of Part D benefits.
- Continued shift in XPOVIO new patient mix³ to 2-4L, approaching 70%, compared to 55% in 2022, with favorable impact on duration
- US XPOVIO Net Product Revenue guidance of \$100-\$120M in 2024

FINANCIAL HIGHLIGHTS AND MILESTONES



4Q and FY 2023 Financial Results

Statements of Operations (\$ millions)	4Q 2023	4Q 2022	FY 2023	FY 2022
Total Revenue	\$33.7	\$33.6	\$146.0	\$157.1
XPOVIO Net Sales	25.1	31.1	112.0	120.4
License and Other Revenue	8.7	2.5	34.0	36.6
Total Operating Expenses	\$71.6	\$67.4	\$275.6	\$299.3
Cost of Sales	1.5	1.9	4.9	5.2
Research and Development Expenses	39.4	30.9	138.8	148.7
Selling, General & Administrative Expenses	30.7	34.6	131.9	145.4
Net Loss	\$41.8	\$38.5	\$143.1	\$165.3
Net Loss per share	\$0.36	\$0.43	\$1.25	\$2.02
Balance Sheet (\$ millions)	Dec 31, 2023	Dec 31, 2022		
Cash, Cash Equivalents Restricted Cash and Investments	\$192.4	\$279.7		

2024 Financial Guidance

- Total Revenue of \$140-\$160 million
- U.S. XPOVIO Net Product Revenue of \$100-\$120 million
- R&D and SG&A Expenses of \$260-\$280 million, including estimated non-cash stock compensation of ~ \$20-\$25 million
- Cash runway expected to be sufficient to fund planned operations into late 2025*

Richard Paulson
Chief Executive Officer

CLOSING REMARKS



Accelerating Innovation and Growth Strategy with Key Milestones in 2024 and 2025

Multiple Myeloma

- ❑ Leverage commercial capabilities and grow XPOVIO (2024)
- ❑ Continuation of global launches (2024)
- ❑ Report data on XPOVIO pre/post T cell therapy (2024)
- ❑ Report top line results from EMN29 trial (1H 2025)

Endometrial Cancer

- ❑ Continue to present exploratory updated results from the *TP53* subgroup from the SIENDO trial at medical conferences (2024)
- ❑ Complete enrollment in pivotal EC-042 Phase 3 trial in *TP53* wild-type EC (2H 2024)
- ❑ Report top-line results from pivotal EC-042 Phase 3 trial in *TP53* wild-type EC (1H 2025)

Myelofibrosis

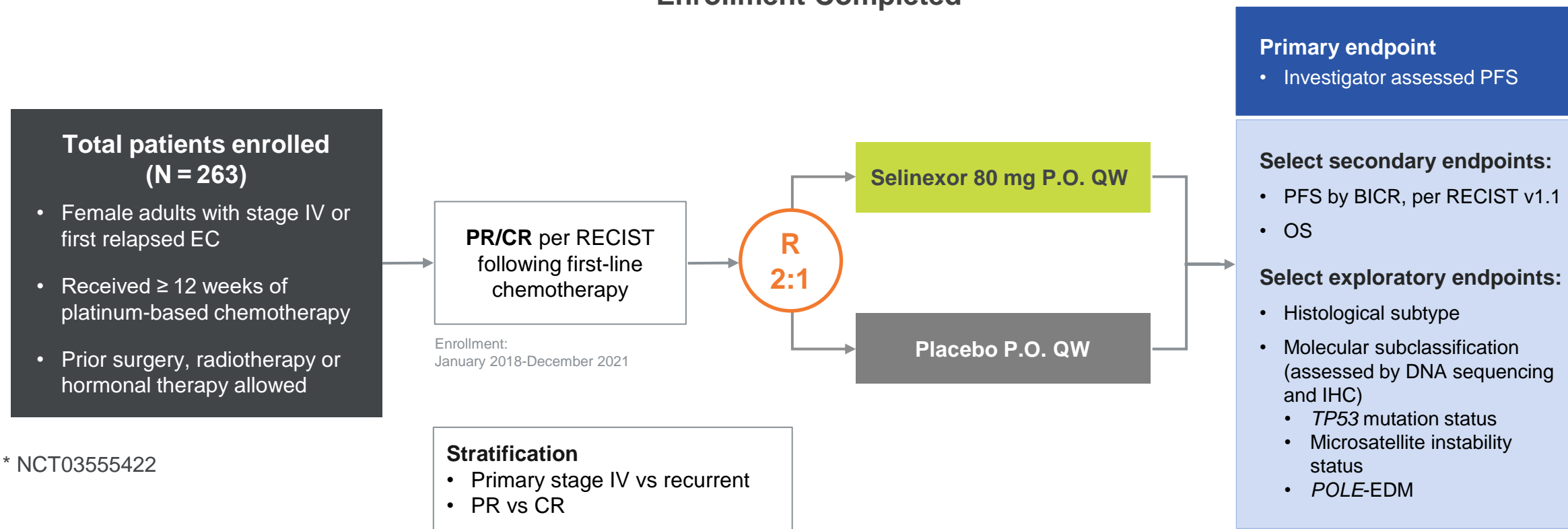
- ❑ Report updated results in Phase 1 trial of selinexor + ruxolitinib in treatment-naïve MF (2024)
- ❑ Report preliminary data from MF-044 Phase 2 study with single agent selinexor in JAKi naïve MF with platelet counts below $50 \times 10^9/L$. (2H 2024)
- ❑ Report top-line results from Phase 3 trial of selinexor + ruxolitinib in treatment-naïve MF (2H 2025)



APPENDIX

SIENDO*: A Randomized Double-Blind, Phase 3 Trial of Maintenance with Selinexor / Placebo after Combination Chemotherapy for Patients with Advanced or Recurrent Endometrial Cancer^{1,2}

Enrollment Completed



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.

BICR, blinded independent central review; CR, complete response; EDM, exonuclease domain mutation; IHC, immunohistochemistry; MSI, microsatellite instability; OS, overall survival; PFS, progression-free survival; PO, per oral; POLE, polymerase epsilon; PR, partial response; QW, once weekly; R, randomized; RECIST, response evaluation criteria in solid tumors; TP53, tumor protein 53 gene