Karyopharm® Therapeutics

A Commercial-Stage Pharmaceutical Company Pioneering Novel Cancer Therapies

March 2024

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 Annual Report on Form 10-K for the year ended December 31, 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.

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]**

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.

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

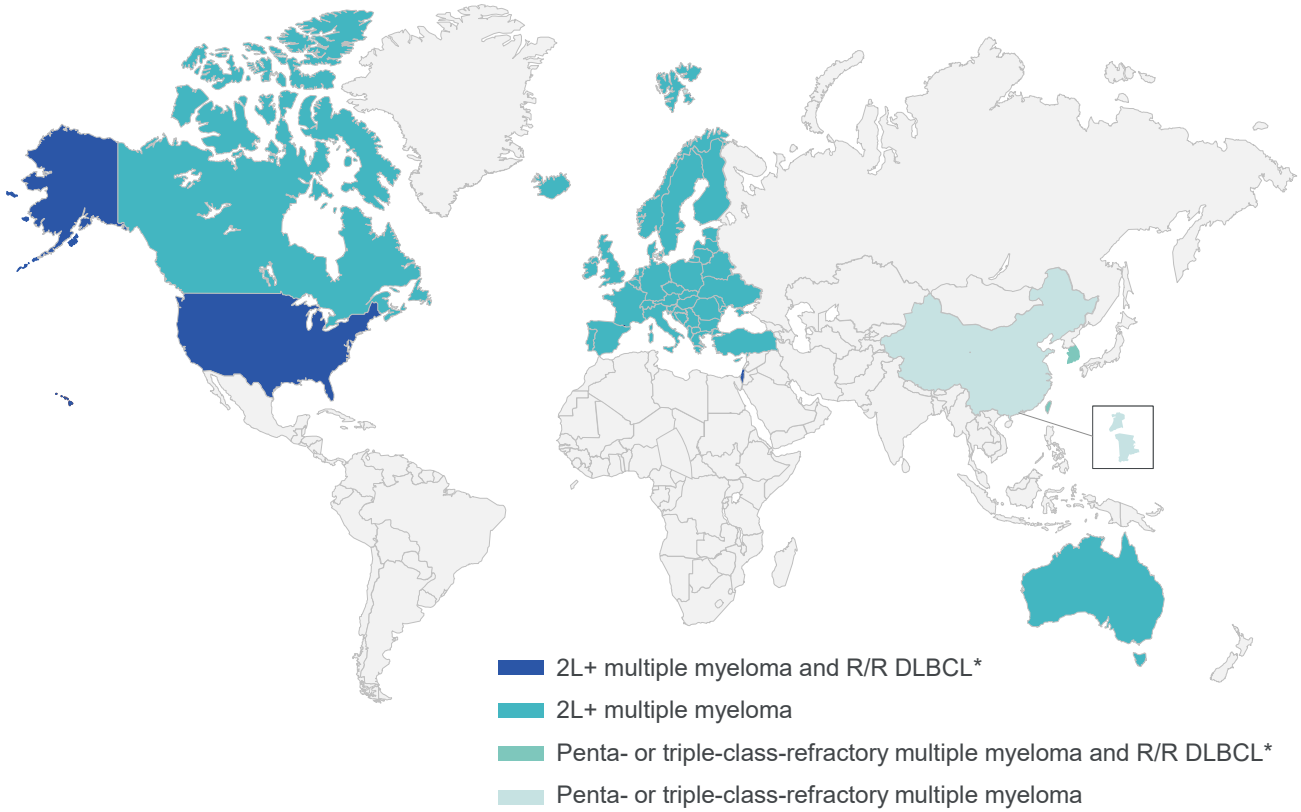
Multiple Myeloma (MM)

- ❑ Continued XPOVIO shift to earlier lines, with patient mix ~70% in the 2-4L
- ❑ Update from NCCN guidelines to list XVd[1] 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

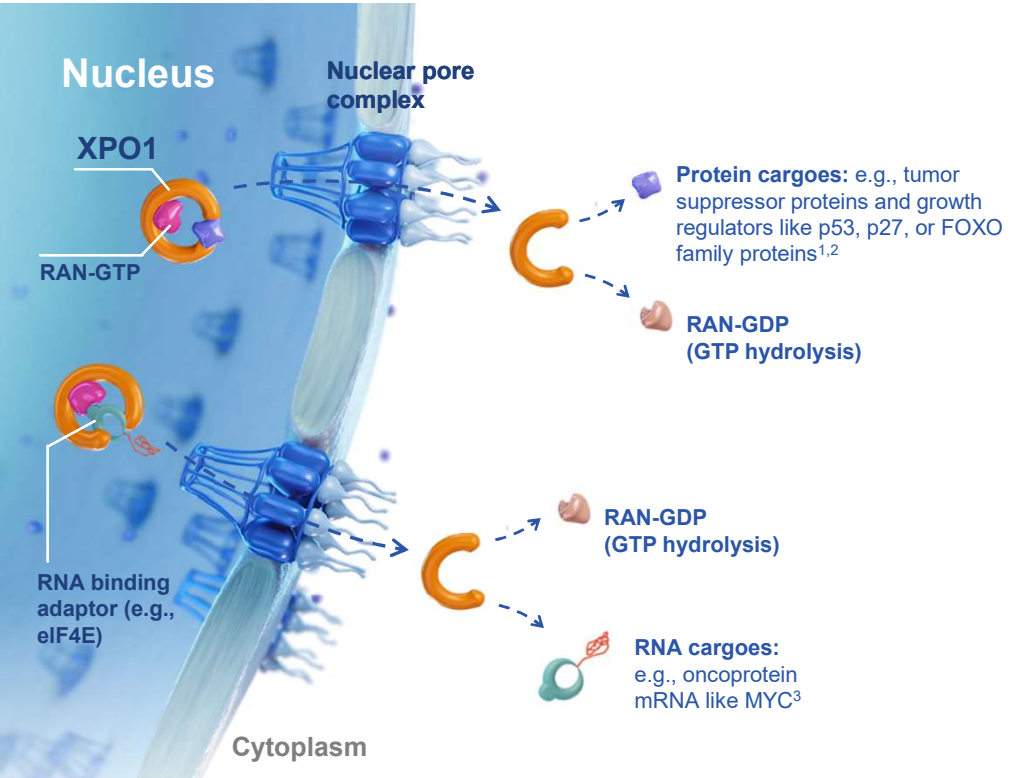
1. Xpovio + Velcade + dexamethasone 2. Pomalidomide + dexamethasone 3. White et al, EHA 2023

Global Launches to Continue in 2024 Building On XPOVIO® /NEXPOVIO® Approvals in Over 40 Countries with Potential to Expand Across Multiple Indications

Country/Region	Indication(s)	Partner
Approvals		
United States		–
Europe[1]		Menarini
UK		Menarini
Mainland China		Antengene
South Korea		Antengene
Australia		Antengene
Singapore		Antengene
Canada		Forus
Israel		Neopharm
Taiwan		Antengene
Hong Kong		Antengene
Macau		Antengene



* DLBCL approved in the U.S. under accelerated approval pathway
1. The 27 countries comprising the European Union, plus Iceland, Norway, Northern Ireland and Lichtenstein.



Exportin 1 (XPO1) transports proteins and protein-RNA complexes out of the nucleus

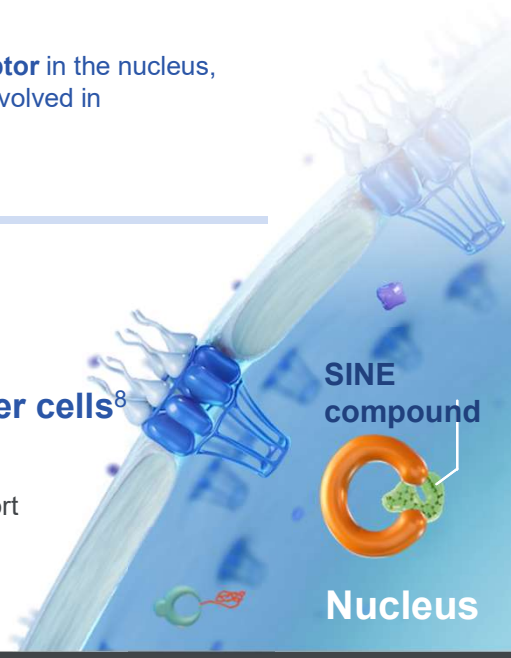
Adapted from Azizian NG, et al (2020)

Selinexor and Eltanexor (SINE compounds) selectively inhibit nuclear export by binding XPO1

1. Increases nuclear levels of **tumor suppressor proteins** and their activation[4,5]
2. Traps **oncoprotein mRNA** in the nucleus, leading to reduced oncoprotein levels[6]
3. Retains **activated glucocorticoid receptor** in the nucleus, leading to altered expression of genes involved in inflammatory pathways[7]

Reduced proliferation and **increased apoptosis of cancer cells**[8]

SINE: Selective inhibition of nuclear export



MYC, MYC proto-oncogene; eIF4E, Eukaryotic translation initiation factor 4E; FOXO, forkhead box, sub-group O; p27, cyclin-dependent kinase inhibitor 1B; p53, tumor protein 53; RAN, RAS-related nuclear protein; GDP, guanosine diphosphate; GTP, guanosine triphosphate

1. Azizian NG, et al. J Hematol Oncol. 2020;13(1):61. doi:10.1186/s13045-020-00903-4; 2. Das A, et al. Exp Hematol Oncol. 2015;4:7. doi:10.1186/s40164-015-0002-5.; 3. Culjkovic-Kraljacic B. Cell Rep. 2012;2(2): 207-15. doi: 10.1016/j.celrep.2012.07.007. 4. Turner JG, et al. Biochem Pharmacol. 2012 Apr 15;83(8):1021-32. doi: 10.1016/j.bcp.2011.12.016. 5. Azmi AS, et al. Nat Rev Clin Oncol. 2021 Mar;18(3):152-169. doi: 10.1038/s41571-020-00442-4. 6 Kashyap T et al, Oncotarget. 2018 Jul 20;9(56):30773-30786. doi: 10.18632/oncotarget.25637; 7. Argueta C, et al. Oncotarget. 2018 May 22;9(39):25529-25544. doi: 10.18632/oncotarget.25368. doi:10.1016/j.clml.2018.03.003; 8. Sun Q, et al. Signal Transduct Target Ther. 2016;1:16010. doi:10.1038/sigtrans.2016.10

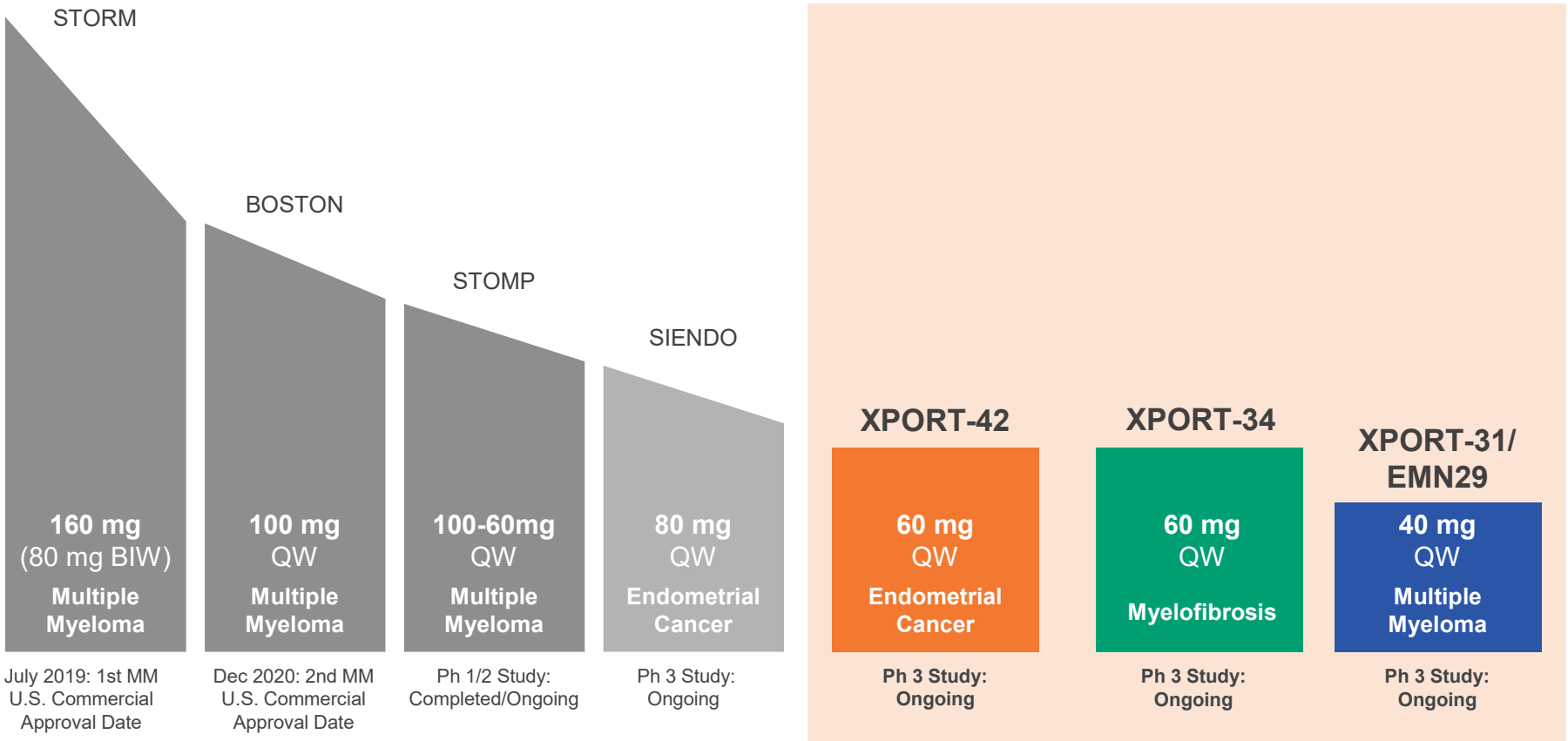
Focused High Potential Pipeline with 3 Pivotal Studies Across Cancers With High Unmet Needs

	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

1. EMN29 Study: Sponsored by European Myeloma Network. 2. Versus elotuzumab, pomalidomide, and dexamethasone. 3. With option to add JAK inhibitors. 4. Planned initiation in 1H 2024. 5. For supply of pacritinib 6. To be initiated as an arm in the STOMP trial 7. XPORT-DLBCL-030 is a Phase 2/3

Optimizing Selinexor Dose to Improve Patient Experience and Overall Benefit

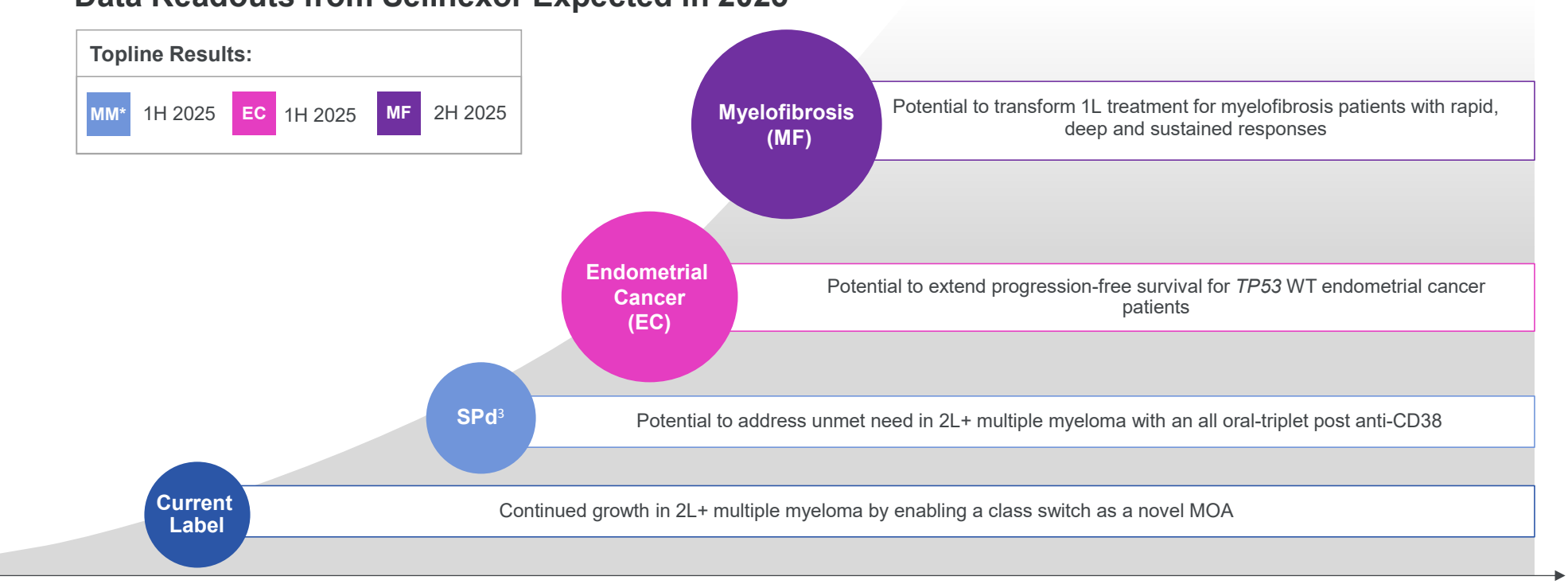


Positioned for Success with 3 Pivotal Studies in Indications with Total US Potential of ~$2B Annual Peak Revenues[1,2]

Data Readouts from Selinexor Expected in 2025

Topline Results:

MM* 1H 2025 | EC 1H 2025 | MF 2H 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.

MYELOFIBROSIS

Selinexor Has the Potential to Define a New Treatment Paradigm in MF[1]

Treatment Landscape and Unmet Need

Population living with MF:

- ~20,000 in the U.S[2]; ~17,000 in EU[2]

No other approved class of therapy other than JAK inhibitors

- Ruxolitinib generates over $1 billion[3] 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 ruxolitinib[4]
- <50% achieve TSS50[4]

Selinexor

- ✓ **XPO1 inhibition is a novel and potentially fundamental mechanism in MF**
- ✓ **Synergism with ruxolitinib observed in preclinical data[5]**
- ✓ **Rapid, deep and sustained spleen response, robust symptom improvement and rapid, sustained cytokine reduction across all subgroups[1]**
- ✓ **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.

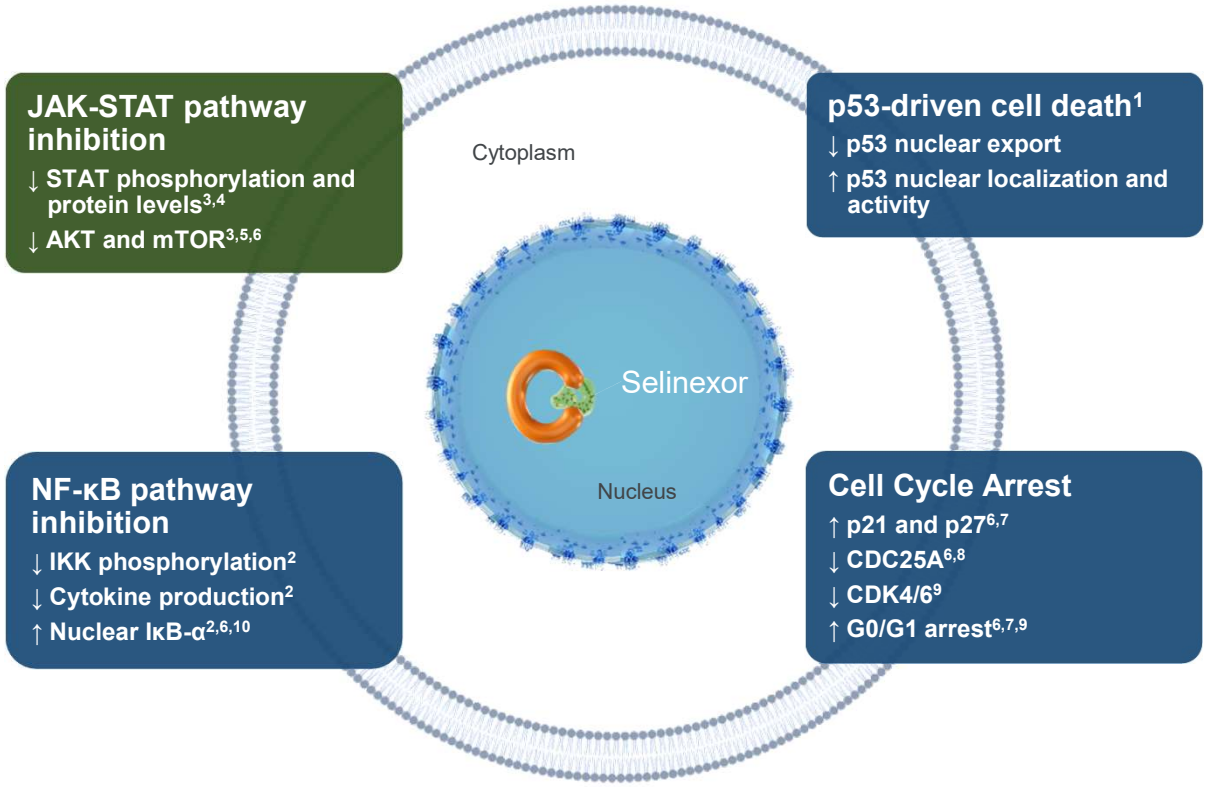
1. Based on selinexor+ruxolitinib Ph 1 results using data cut as of August 1,2023
2. Mehta et.al. Leuk Lyphoma 2014 Mar ;55(3):595-600 and US Census data; Clarivate/DRG Epidemiology Data (2022 figures, pub 2019)
3. Incyte Q4 2023 Results
4. MANIFEST and TRANSFORM Phase 3 studies, ASH 2023
5. Al-Ali, et al. Hematologica. 2016;101(9):1065

XPO1 Inhibition is a Potentially Fundamental MoA in MF that Targets Both JAK-STAT and non-JAK-STAT Pathways[1-10]

Representing Potentially Additive or Synergistic Activity When Dosed in Combination

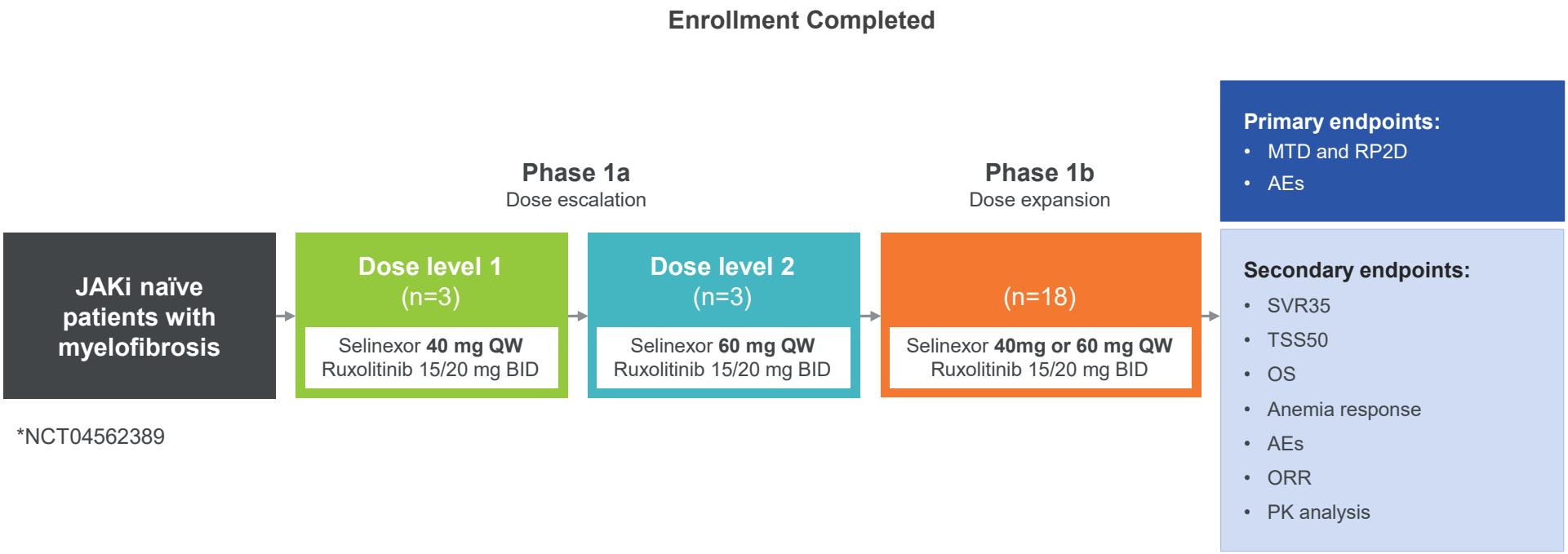
Selinexor inhibits XPO1-mediated nuclear cargo protein export leading to:

- Increased malignant cell death[1]
- Decreased malignant cell proliferation[1]
- Reduced inflammation[2]



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.

Phase 1 Study (XPORT-MF-034*) Evaluating Selinexor in Combination with Ruxolitinib in Treatment-naïve Myelofibrosis



*NCT04562389

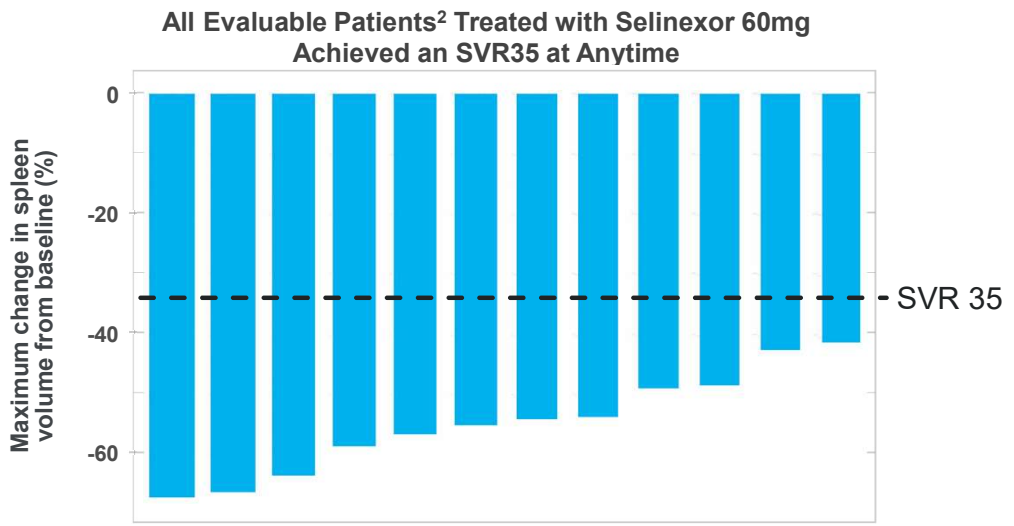
The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the U.S. FDA or any other regulatory authority.

AE, adverse event; BID, twice a day; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; QW, once weekly; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SVR35, spleen volume reduction of at least 35%; TSS50, total symptom score reduction ≥ 50%.

Rapid and Deep SVR35 Achieved with Selinexor 60mg + Ruxolitinib in Ph1 Trial

		SVR35
Population	**Timepoint**	**Selinexor 60mg +ruxolitinib 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 ≥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%)

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. Two patients discontinued prior to Week 24
2. n=12; one patient discontinued prior to week 12; one patient with missing data at week 12 who subsequently discontinued prior to week 24

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	**7/9[4] (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.

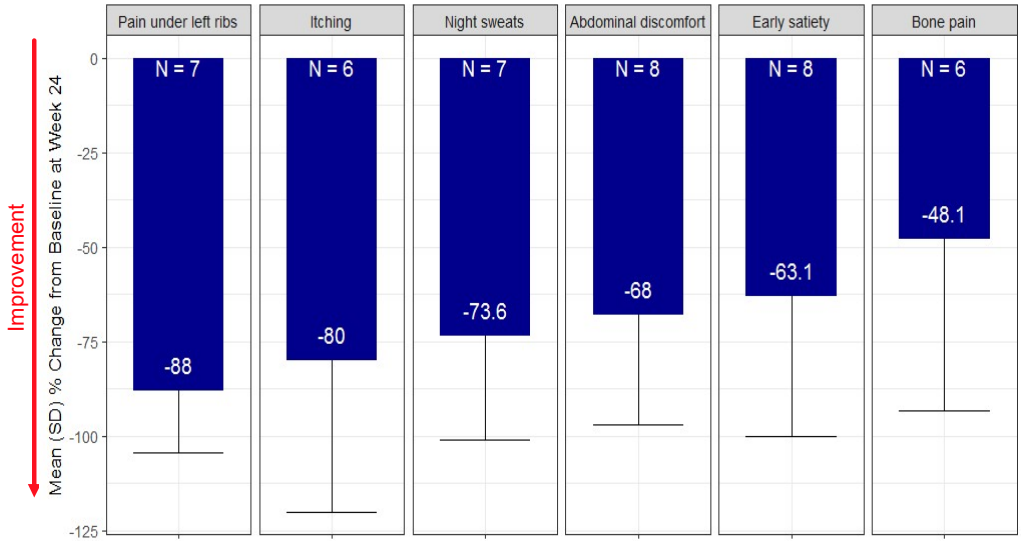
Data cut August 1, 2023

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

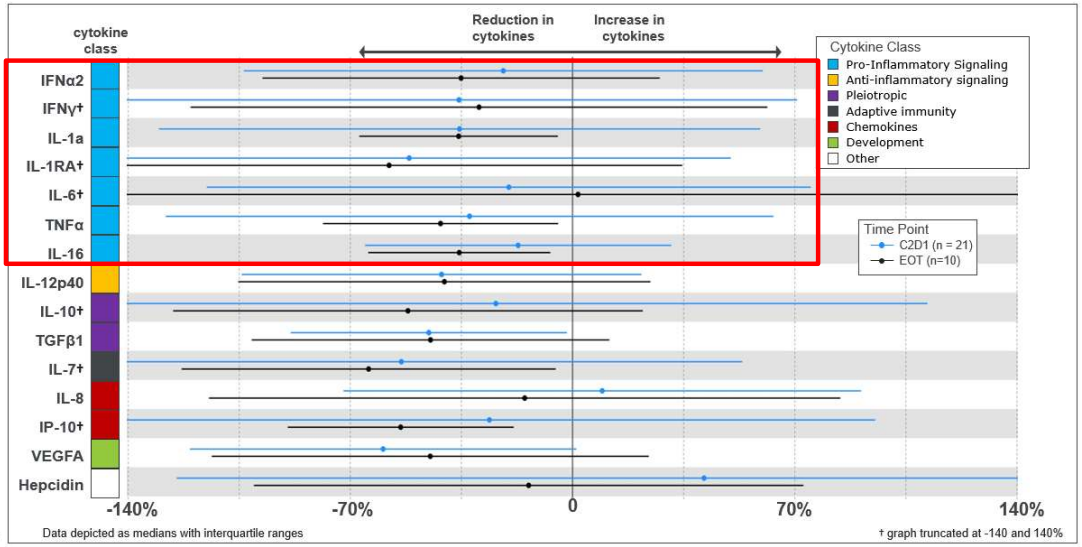
Robust Symptom Improvement Observed with Selinexor + Ruxolitinib

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

Mean % Change at Week 24 in Symptom Domains[1]



Plasma Change in Cytokines[2]



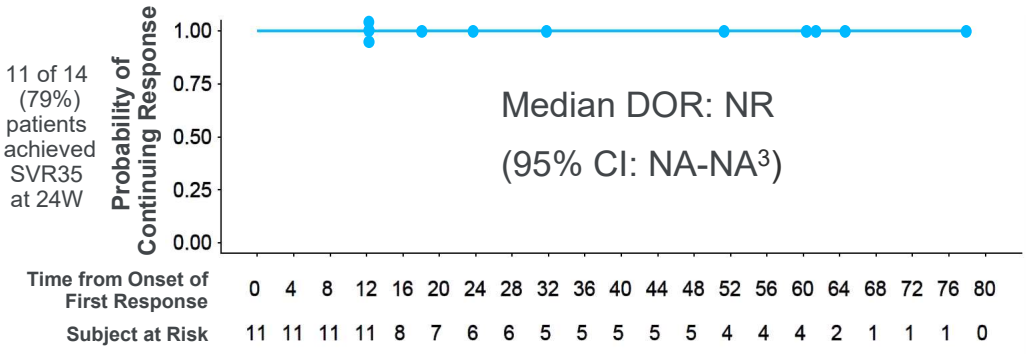
C2D1: Week 4 (blue) ; EOT: End of treatment (black)

Data cut August 1, 2023

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, TFGB, and Hepcidin 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

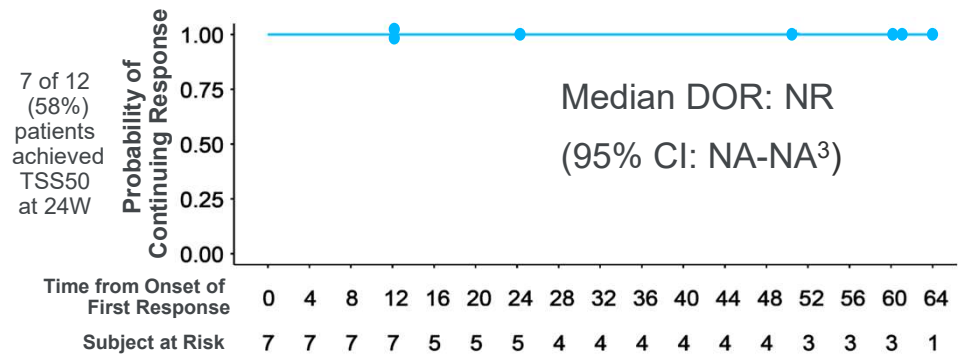
No Progression for SVR35 or TSS50 Responders[1,2] on Selinexor 60mg + Ruxolitinib at Data Cutoff of August 1, 2023

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



Median duration of follow-up: 32 weeks (12, 78)

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



Median duration of follow-up: 51 weeks (12, 64)

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

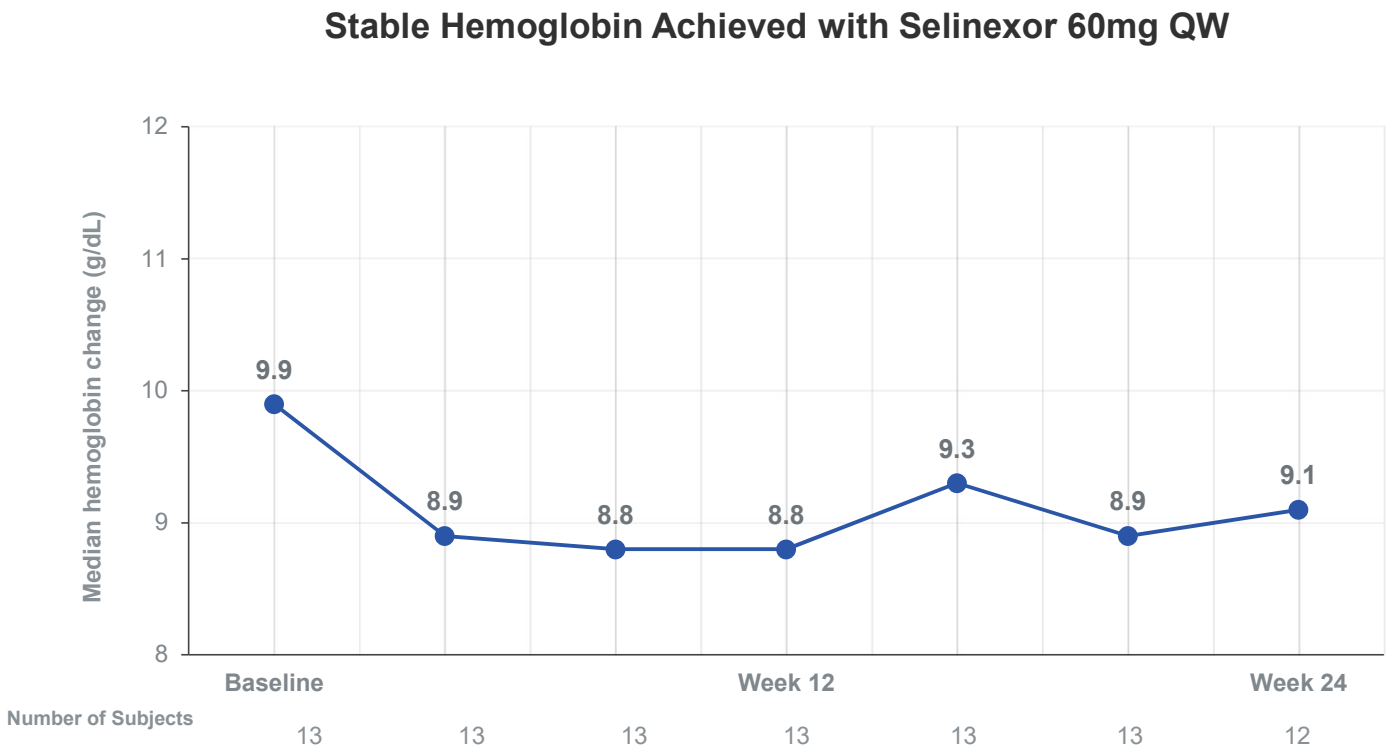
1. SVR progression defined as less than or equal to 35% spleen volume reduction from baseline and more than 25% increase in spleen volume from nadir, assessed radiographically.
2. TSS progression defined as a total symptom score that is equal to or exceeds the baseline value.
3. Not Applicable.

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

* 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



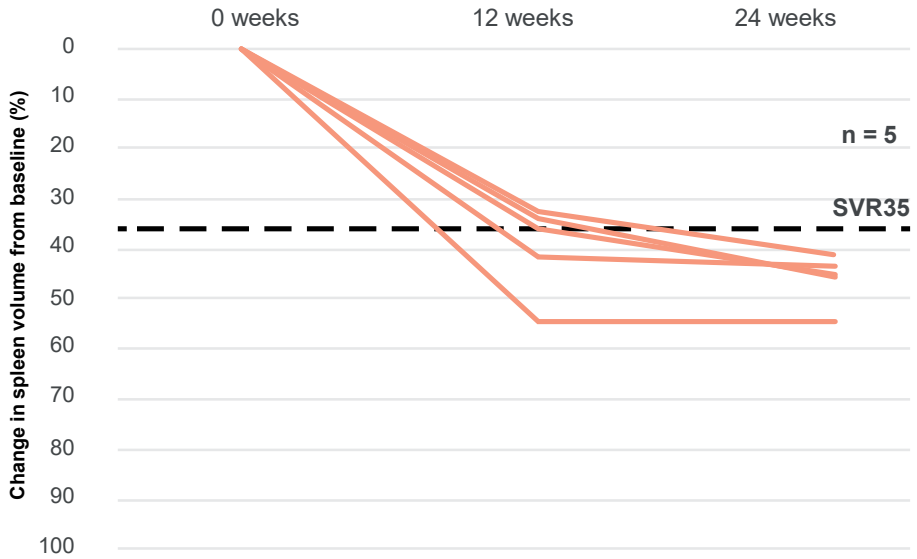
The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the U.S. FDA or any other regulatory authority for use in myelofibrosis.

Data cut August 1, 2023

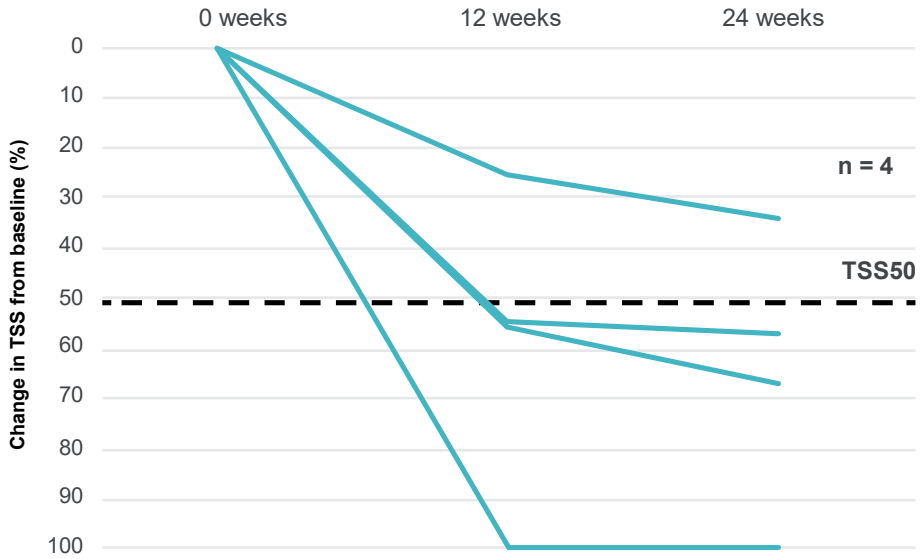
Efficacy with Selinexor in Combination with Suboptimal Dose of Ruxolitinib (≤5 mg*) Further Supports XPO1 as a Fundamental MoA in MF

Retrospective, Exploratory Analysis from Phase 1 Selinexor (60mg) + Ruxolitinib Study (034)

Spleen Volume Reduction



Total Symptom Score Reduction[1]



*Patients received ruxolitinib at ≤ 5 mg BID for at least five out of the first six cycles

"Based on limited clinical data, long-term maintenance at a 5 mg 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.

Data cut August 1, 2023

1. One patient with missing TSS50 score

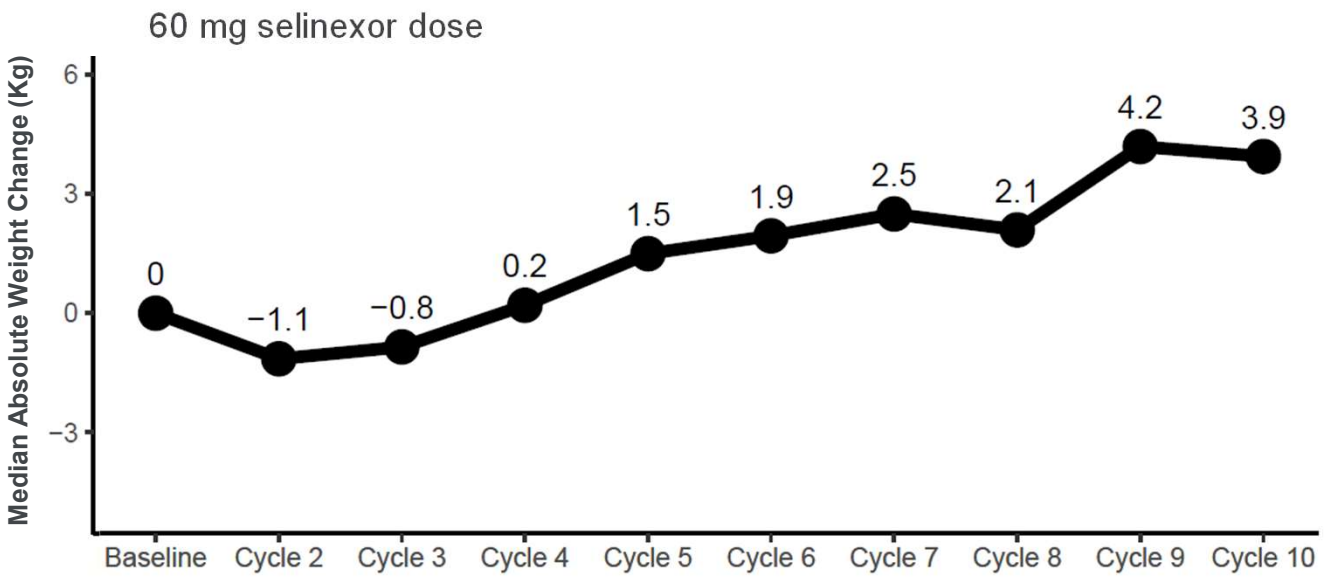
MF-034 Selinexor and Ruxolitinib Phase 1:Treatment Emergent Adverse Events

TEAEs	Selinexor 60 mg QW + ruxolitinib (n = 14)
Any grade (≥ 30% overall), n (%)	
Nausea	11 (78.6)
Anemia	9 (64.3)
Thrombocytopenia	9 (64.3)
Fatigue	8 (57.1)
Constipation	7 (50.0)
Vomiting	7 (50.0)
Dyspnea	5 (35.7)
Headache	5 (35.7)
Hyponatremia	5 (35.7)
Leukopenia	5 (35.7)
Neutropenia	5 (35.7)
Grade 3+ (> 5%), n (%)	
Anemia	6 (42.9)
Thrombocytopenia	4 (28.6)
Back pain	2 (14.3)
Neutropenia	1 (7.1)
Atrial fibrillation	1 (7.1)
Leukopenia	1 (7.1)
Treatment-related AEs leading to treatment discontinuations, n (%)	
Thrombocytopenia, Grade 3	1 (7.1)
Peripheral neuropathy, Grade 3	1 (7.1)

- Treatment related discontinuations due to cytopenias were low (n=1)
- 75% of nausea events were Grade 1
  - One patient experienced Grade 3 nausea (no antiemetic prophylaxis)
- In the 60mg cohort, 64% of patients received one prophylactic antiemetic
  - Amongst the subgroup who received one prophylactic antiemetic, 67% of patients experienced nausea (Grade 1 only) compared to 100% of those who did not receive prophylactic antiemetics (Grades 1-3)

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 Experienced Improved Weight with Selinexor in Combination with Ruxolitinib



- Patients' median weight increase at Week 24 was 3 kg in the 40mg cohort and 2.5 kg in the 60mg cohort
- Despite nausea and vomiting incidence, patients generally did not experience weight loss

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.

Data cut February 24, 2023

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

JOHN MASCARENHAS, MD

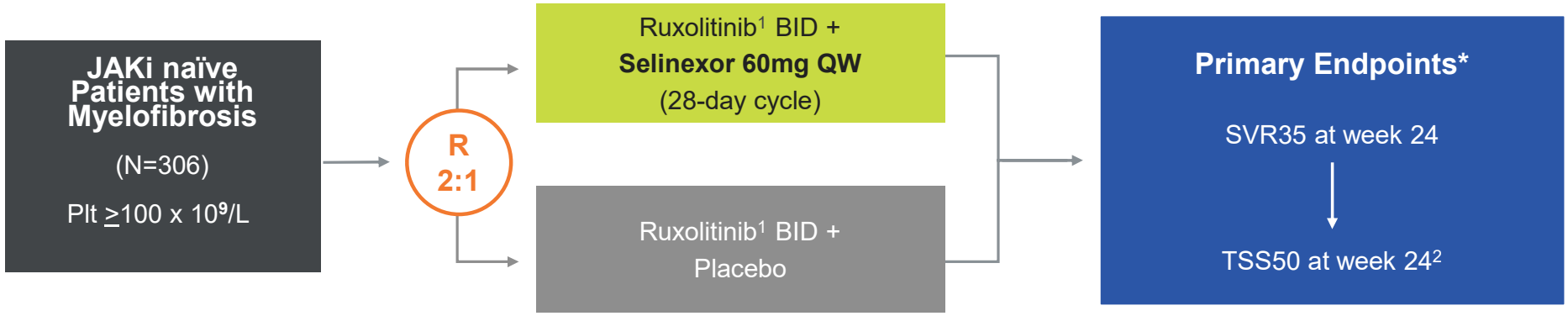
Professor of Medicine at the Icahn School of Medicine at Mount Sinai, Director of the Center of Excellence for Blood Cancers and Myeloid Disorders

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

Endpoints tested sequentially

Randomization stratified by:

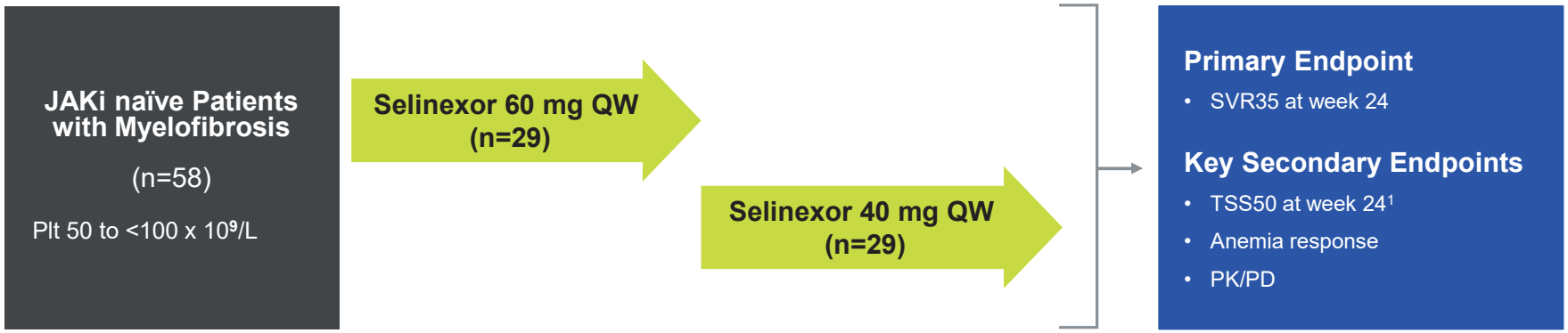
- Dynamic International Prognostic Scoring System (DIPSS) risk category intermediate -1 vs. intermediate -2 or high-risk
- Spleen volume <1800 cm^3 vs. ≥1800 cm^3 by MRI/CT scan
- Baseline platelet counts 100-200 x 10^9/ L vs. >200 x 10^9/L

Top-line Data Expected in 2H 2025

1. Ruxolitinib dose based on platelet count per prescribing information
2. Evaluated in the myelofibrosis assessment form (MFSAF)

Phase 2 XPORT-MF-044* Study Evaluating Selinexor As Monotherapy in JAKi Naïve MF Patients

Study Planned to be Initiated in 1H 2024



* 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	sobi[3]
Add **momelotinib**[3] if plt >50 x10^9/L hemoglobin level is <10 g/dL	

Pacritinib supply agreement with SOBI

1. Evaluated in the myelofibrosis assessment form (MFSAF) 2. Per ruxolitinib label: 5 to 10 mg BID for at least 2 weeks, based on the plt level 3.In the U.S. only 3. For supply of pacritinib

BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; PD, pharmacodynamic; PK, pharmacokinetic; plt, platelet; QW, once weekly; SVR, spleen volume reduction; SVR35, SVR ≥35; TSS50, total symptom score ≥50

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

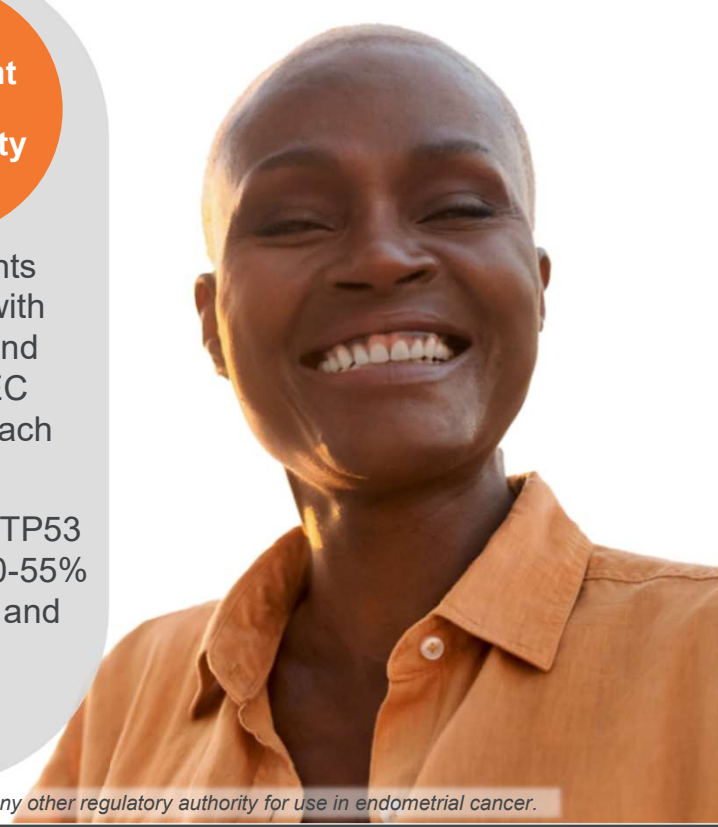
Addressing a Significant Unmet Need

No FDA approved treatments for pMMR[1] (proficient mismatch repair), which represents ~80% of advanced and recurrent EC[2]

Significant Market Opportunity

~16K patients diagnosed with advanced and recurrent EC in the U.S. each year[3]

~ >50% have TP53 WT EC, and 40-55% are TP53WT and pMMR[2,4]

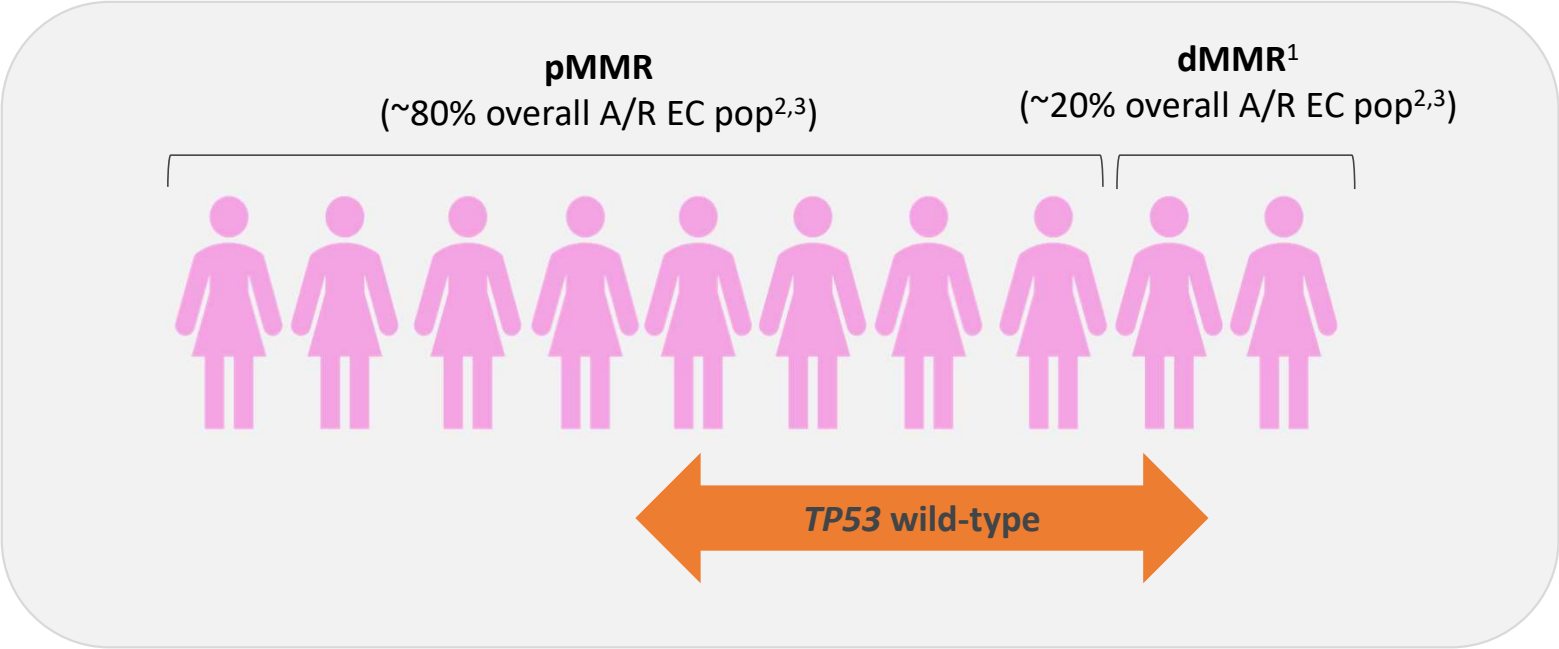


The safety and efficacy of selinexor in endometrial cancer has not been established and has not been approved by the U.S. FDA or any other regulatory authority for use in endometrial cancer.

1. As of to date 2. Mirza, M et al. (2023, October 20-24). 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. Clarivate/DRG Endometrial Carcinoma Epidemiology Dashboard (2022 figures, pub 2020) 4. "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

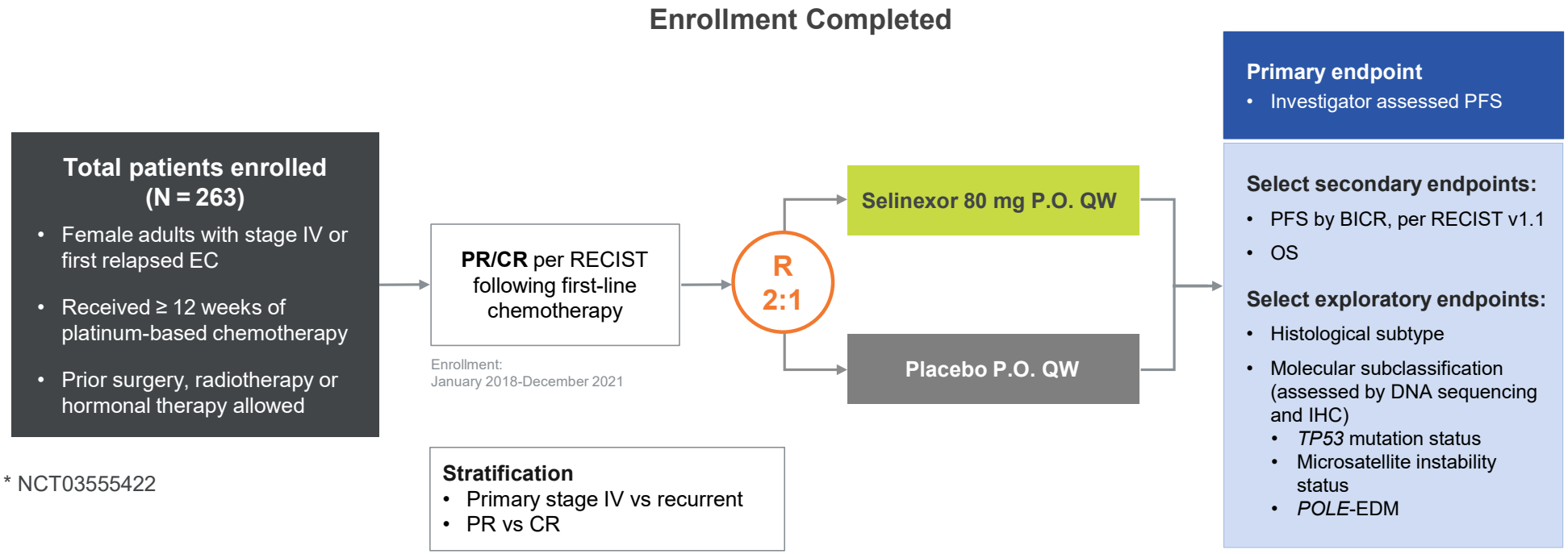
Emerging Role of TP53 and Importance of Molecular Profiling in the Evolving Landscape of Advanced and Recurrent Endometrial Cancer (A/R EC)

Patients Who are Both *TP53* Wild-Type AND pMMR Represent 40-55% of all A/R EC[2,3,4,5]



1. Deficient mismatch repair 2. Mirza, M et al. (2023, October 20-24). 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. Vergote I, et al. J Clin Oncol. 2023 Sep 5:JCO2202906.2023 Oral Selinexor as Maintenance Therapy After First-Line Chemotherapy for Advanced or Recurrent Endometrial Cancer, https://pubmed.ncbi.nlm.nih.gov/37669480/ 4. Slomovitz B et al. Presentation at American Society for Clinical Oncology Plenary Series; July 25, 2023; 5. Leslie KK, et al Gynecol Oncol. 2021 April ; 161(1): 113–121

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]



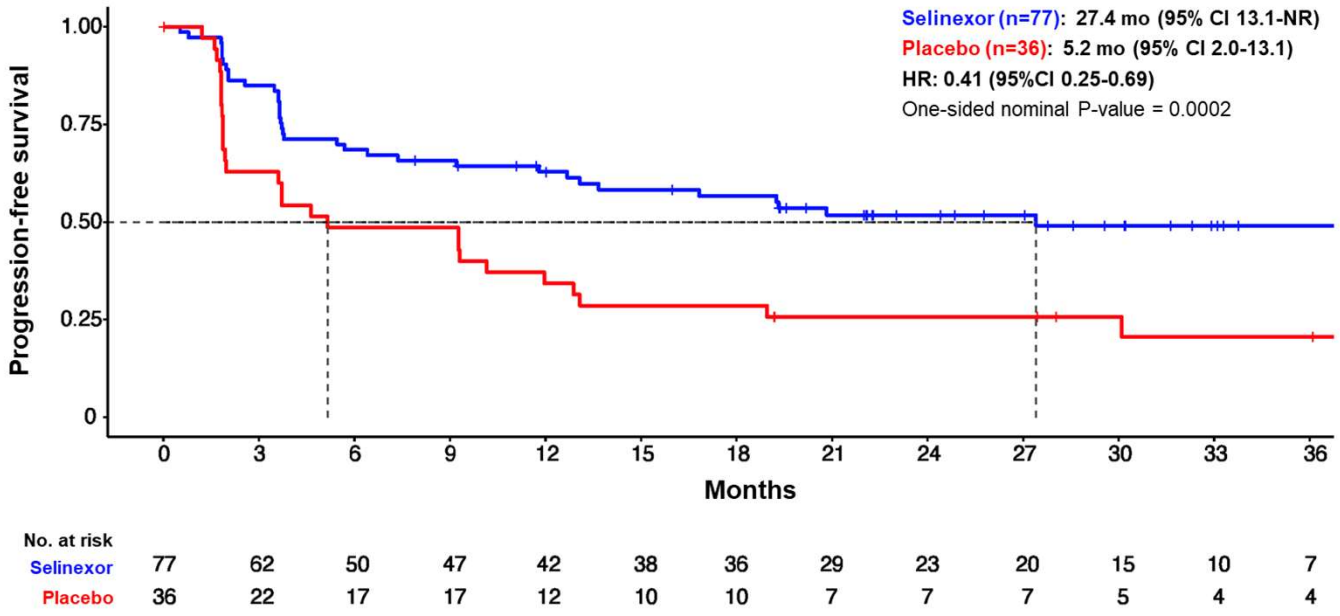
* NCT03555422

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

1. Maintenance With Selinexor/Placebo After Combination Chemotherapy in Participants With Endometrial Cancer [SIENDO] (ENGOT-EN5).Updated May 30, 2023. Accessed June 26, 2023. https://www.clinicaltrials.gov/study/NCT03555422?term=NCT03555422 2. Vergote I, et al. Presentation at: European Society for Clinical Oncology Virtual Plenary; March 17-18, 2022, Abstract VP2-2022.

Updated Data from SIENDO Study[1] Indicate Encouraging Signal of PFS Benefit with Median PFS Benefit > Two Years in *TP53* Wild Type EC



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.

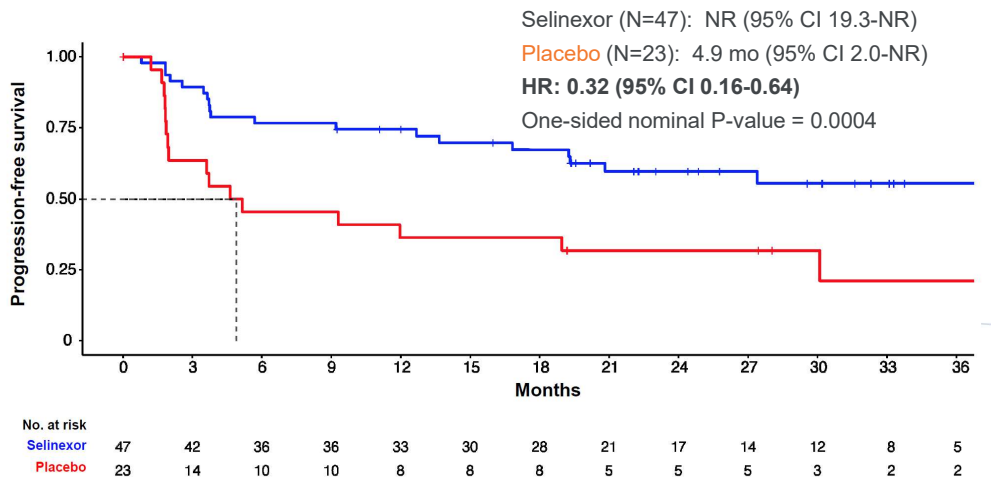
Data cut September 1, 2023

NR, not reached.
1. Pre-specified exploratory TP53wt subgroup from SIENDO trial; data presented at IGCS 2023 Annual Global Meeting

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

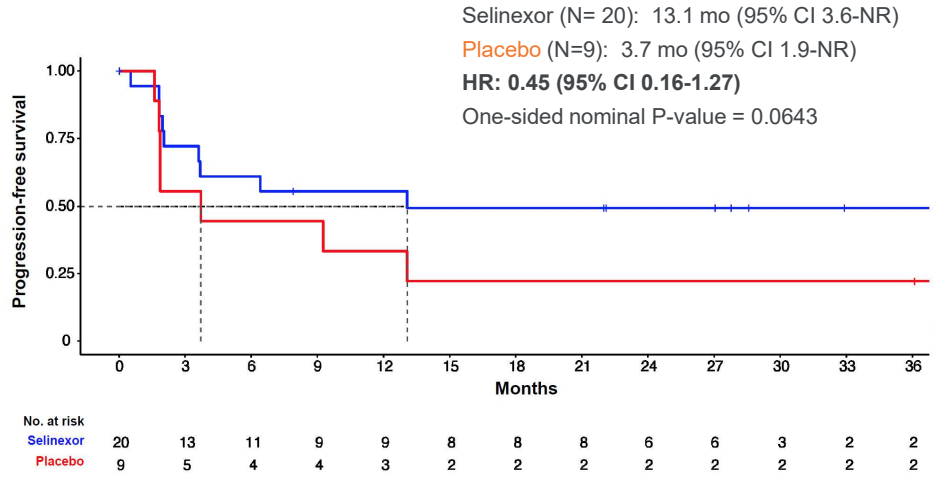
Long Term Follow-Up[1]: PFS in TP53 WT Exploratory Subgroup Based on MMR status

TP53 WT / pMMR (MSS)



Median follow-up: 31.6 months

TP53 WT / dMMR (MSI-H)



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

NR, not reached.

1. Presented at IGCS 2023 Annual Global Meeting

Preliminary Overall Survival Data[1] from SIENDO Shows Encouraging Signal in the *TP53* Wild-Type Exploratory Subgroup

	No. with events (%)	Overall Maturity (%)	Median (95% CI), months	HR (95% CI)	Nominal one-sided p-value	Median follow up (months)
***TP53*wt**						
Selinexor (n=77)	23.4%	26.6%	NR (NR, NR)	**0.76** (0.36-1.59)	0.24	28.9
Placebo (n=36)	33.3%		NR (35.19, NR)			
***TP53*wt/pMMR (MSS)**						
Selinexor (n=47)	23.4%	30.0%	NR (NR, NR)	**0.57** (0.24-1.35)	0.098	31.6
Placebo (n=23)	43.5%		35.19 (28.68, NR)			
***TP53*wt/dMMR (MSI-H)**						
Selinexor (n=20)	10.0%	10.3%	NR (NR, NR)	**0.62** (0.06-6.81)	0.35	27.3
Placebo (n=9)	11.1%		NR (NR, NR)			

Follow Up Data Including Overall Survival To Be Presented in 2024

Data cut September 1, 2023

NR, not reached.

1. Presented at IGCS 2023 Annual Global Meeting

SIENDO Study: Generally Tolerable and Manageable Side Effect Profile

	*TP53*wt			
	Selinexor (N = 76†) n (%)		Placebo (N = 35†) n (%)	
TEAEs*	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Nausea	68 (89.5)	9 (11.8)	12 (34.3)	0 (0.0)
Vomiting	46 (60.5)	2 (2.6)	4 (11.4)	1 (2.9)
Diarrhea	32 (42.1)	3 (3.9)	13 (37.1)	0 (0.0)
Constipation	25 (32.9)	0 (0.0)	14 (40.0)	2 (5.7)
Asthenia	27 (35.5)	4 (5.3)	9 (25.7)	0 (0.0)
Fatigue	27 (35.5)	6 (7.9)	7 (20.0)	0 (0.0)
Thrombocytopenia	32 (42.1)	8 (10.5)	1 (2.9)	0 (0.0)
Decreased appetite	27 (35.5)	0 (0.0)	1 (2.9)	0 (0.0)
Neutropenia	26 (34.2)	14 (18.4)	2 (5.7)	0 (0.0)
Anemia	25 (32.9)	5 (6.6)	1 (2.9)	0 (0.0)
Abdominal pain	20 (26.3)	0 (0.0)	5 (14.3)	1 (2.9)
TEAEs leading to:				
Discontinuation	12 (15.8)		0	
Death	0		1 (2.8)	

*TEAEs in ≥ 20% patients; TEAE incidence and severity were generally similar in the *TP53mut/abn* subgroup.; † Two patients did not receive treatment (n=1 selinexor; n=1 placebo) and were excluded from this analysis.

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

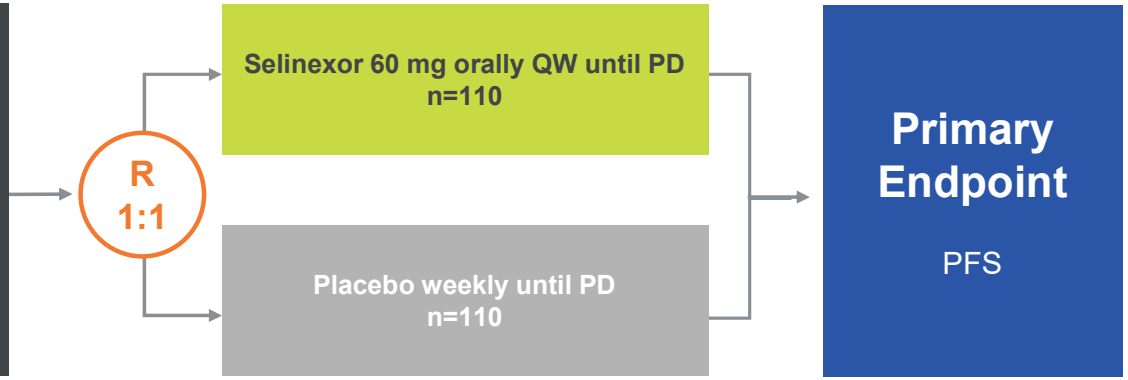
TP53 Wild-type Status is Assessed by Companion Diagnostic Partner Foundation Medicine[1]

Study in Collaboration with ENGOT[2] and GOG[3]

Key Eligibility

TP53 wild-type endometrial cancer[1]

- Primary stage IV or recurrent EC
- Received at least 12 weeks of platinum-based therapy +/- immunotherapy
- In partial response (PR) or complete response (CR) to chemotherapy



*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.

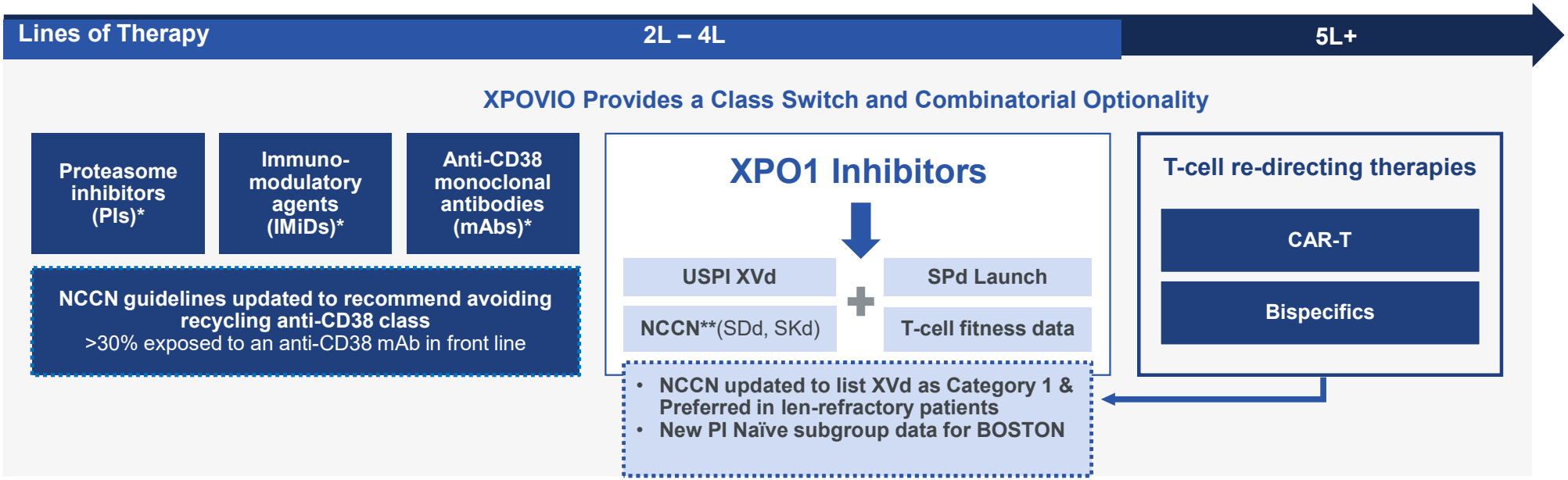
Top-line Data in 1H 2025

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

1. Utilizing Foundation Medicine's tissue-based comprehensive genomic profiling test to identify TP53 status
2.European Network for Gynaecological Oncological Trial groups
3. Gynecologic Oncology (GOG) Foundation

MULTIPLE MYELOMA

Differentiated Position of XPOVIO as a Novel and Effective Class of Therapy in 2-4L MM with Positive NCCN Guideline Updates



Community setting (~70% of MM patients)	Academic setting (~30% of MM patients)

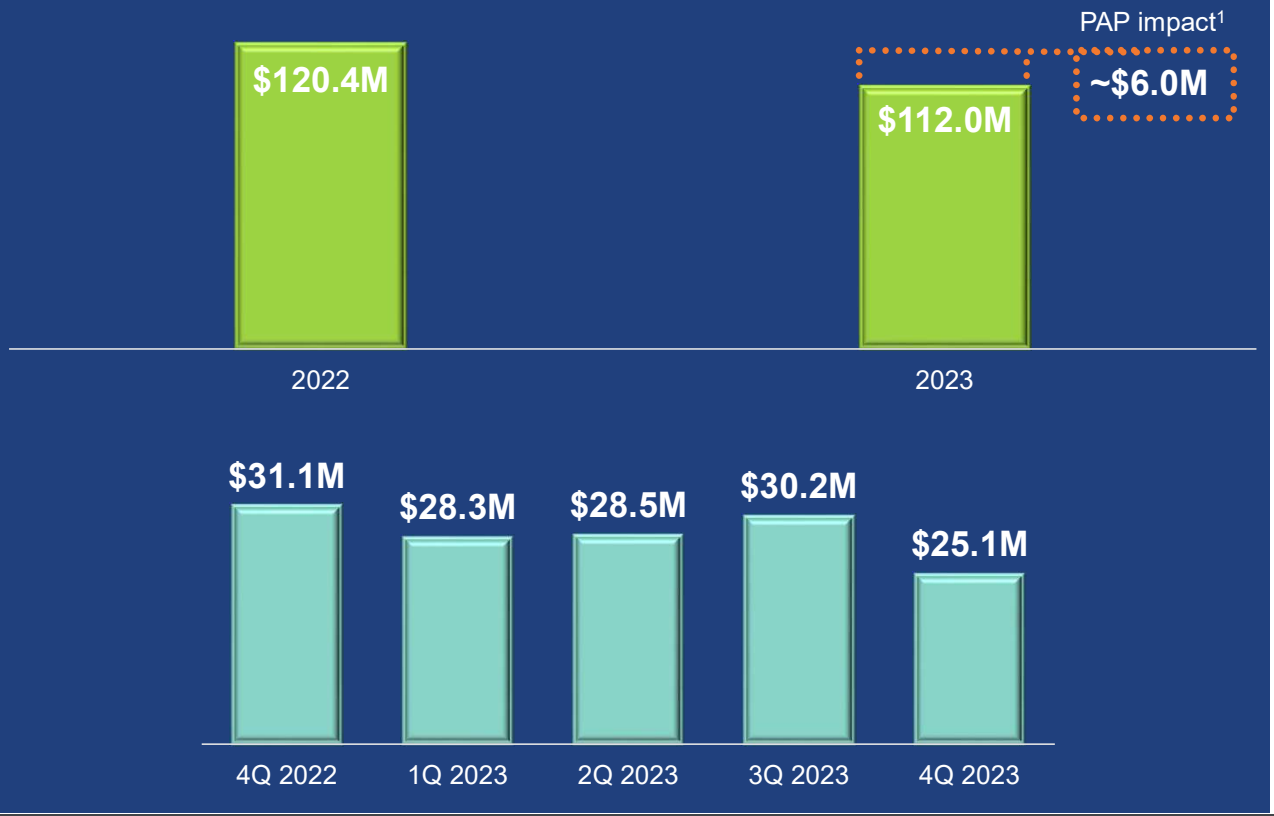
XPOVIO combinations other than XVd and Xd will not be promoted by Karyopharm, but may be considered for future indication updates.

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.

+dexamethasone
** NCCN Guideline inclusion for SPd, SDd and SKd

XPOVIO Update: 4Q 2023 and FY 2023

Net Product Revenue in 2023 Adversely Impacted by Increase in PAP[1], Higher Gross-To-Net and Increased Competition

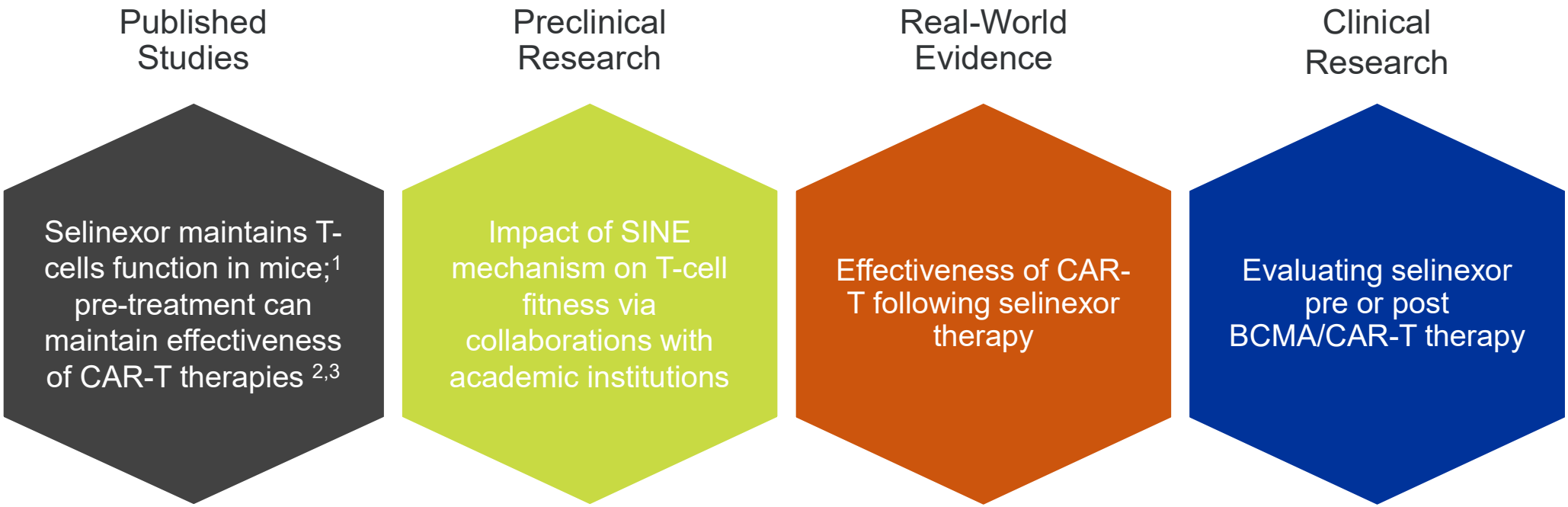


4Q and FY 2023 Highlights

- XPOVIO Net Product Revenue of $112M and $25M for FY 2023 and Q4 2023, respectively
- Demand[2] growth in the community setting in FY 2023 vs 2022, accounting for ~ two thirds of XPOVIO net product revenue
- Demand[2] 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 mix[3] 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[1]

1. Patient Assistant Program 2. Includes PAP and commercial demand 3. Based on Komodo claims data accessed in November 2023. This guidance was provided by the Company on February 29, 2024 and is not being updated as it is representative of information as of that date only.

Generating Evidence on the Role and Effectiveness of Selinexor pre and post T-cell Mediated Therapies



1. Tyler PM et al., Mol Cancer Ther. 2017 Mar;16(3):428-439.
2. Wang S et al., Oncol Rep. 2021 Aug;46(2):170.
3. Stadel R et al., Blood (2022) 140(Supplement 1): 7413–7414, ASH Annual Meeting 2022

SPd, As an All-Oral Combination, Has the Potential to Benefit Significant Number of Patients Across the Multiple Myeloma Treatment Journey Upon Approval[1]

1. **Commonly Used Backbone Post Anti-CD38**
   SPd as therapy of choice following anti-CD38 mAbs will drive use in earlier lines; Pomalyst®, a commonly used IMiD, generates >$2B in revenues annually in the U.S.[2]

2. **All Oral Combination, Potentially T-cell Sparing**
   SPd has the potential to be the only approved all-oral triplet providing convenience for patients

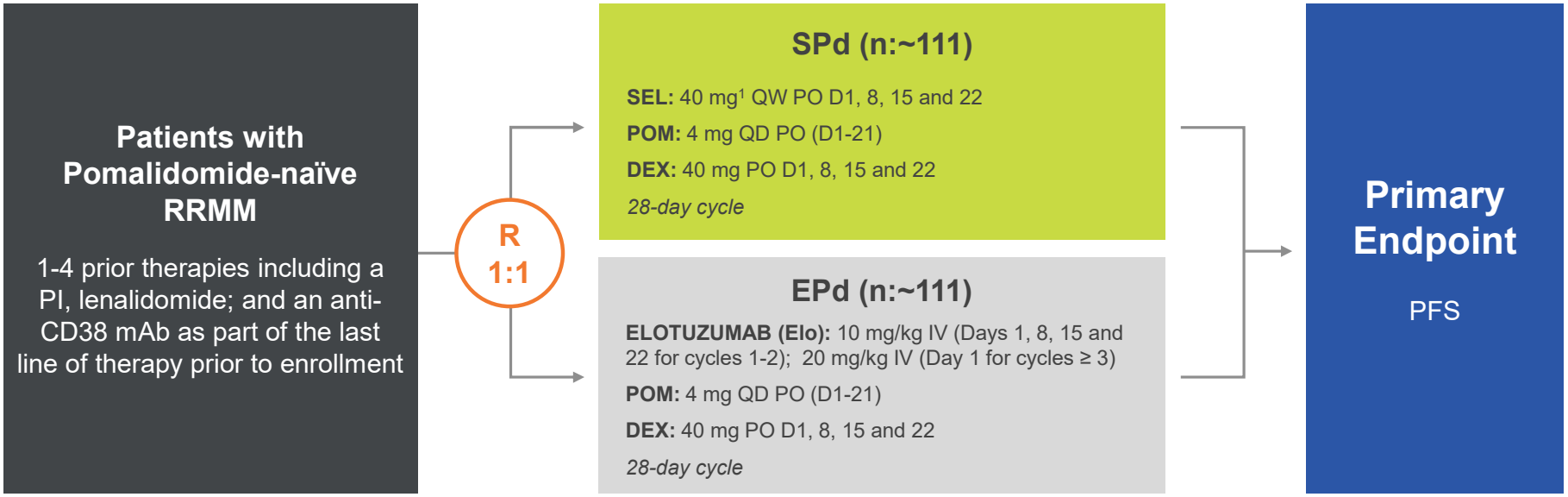
3. **Lower Dose**
   SPd (40mg selinexor) QW dose achieved a median PFS of 18.4months[3] with improved tolerability

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

1. Depending on a successful outcome from 031/EMN29 registrational study supporting label extension of Selinexor-Pomalidomide-dex (SPd) at a 40mg dose
2. BMS financial results 3. n=28; data on file from Study 28

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

1. 40mg 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

PARTNERSHIPS, FINANCIAL HIGHLIGHTS AND MILESTONES

Strategic Partnerships Driving Expansion of Our Global Footprint

Commercial Partnerships Serving Key Global Markets

ANTENGENE

AsiaPac

the MENARINI group

EU, LatAm, Middle East & Africa

NEOPHARM

Israel

FORUS THERAPEUTICS

Canada

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[1]

- 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[2]

1. This guidance was provided by the Company on February 29, 2024 and is not being updated as it is representative of information as of that date only
2. * Excluding repayment of the principal of the Company's convertible notes due in October 2025

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 × 10^9/L. (2H 2024)
- ❑ Report top-line results from Phase 3 trial of selinexor + ruxolitinib in treatment-naïve MF (2H 2025)