Karyopharm® Therapeutics

Third Quarter 2022 Financial Results & Business Update

November 3, 2022

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**

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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 financial guidance for full year 2022; Karyopharm's expected cash runway; the ability of selinexor or eltanexor to treat patients with multiple myeloma, diffuse large B-cell lymphoma, myelofibrosis, myelodysplastic syndromes, solid tumors and other diseases; and expectations related to future clinical development and potential regulatory submissions of 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 June 30, 2022, which was filed with the Securities and Exchange Commission (SEC) on August 4, 2022, and in other filings that Karyopharm may make with the SEC in the future. Any forward-looking statements contained in this press release 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, eltanexor, KPT-9274 and verdinexor 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

Karyopharm® Therapeutics

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

Positioned for Expanded Growth

XPOVIO/ NEXPOVIO
Approved in Multiple Myeloma (MM) and DLBCL

- Expanded global footprint with regulatory approvals in 40 countries
- $155-$165m total revenues expected in 2022
- Moving into earlier lines of therapy in MM

Targeted Expansion of Indications with Focused Clinical Pipeline; Optimizing Dose for Efficacy and Tolerability

- Compelling clinical data in Endometrial Cancer, Myelofibrosis and Myelodysplastic Syndrome (MDS)

Experienced Leadership

- Leadership with a focus on accelerating commercial growth and enhancing mid-to-late stage clinical development

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Third Quarter 2022 and Recent Highlights

Expanding on Multiple Myeloma Foundation Globally with Continued XPOVIO Growth

3Q22 U.S. XPOVIO Net Product Revenue: $32.0M; 20% YoY growth

- Increasing use of XPOVIO in earlier lines with strong growth in the U.S. Community setting
- Recent commercial launches by partner Menarini Group in Germany and Austria following full EU approval for NEXPOVIO in July expanding indication to 2L+

Advancing Clinical Pipeline in Core Indications

Endometrial Cancer (EC): Initiation of Pivotal Phase 3 Study in *TP53* wild-type advanced or recurrent *EC*

- Utilizing Foundation Medicine's tissue-based next generation sequencing test to identify patients whose tumors are *TP53* wild-type

Myelofibrosis: Results from Phase 1 XPORT-MF-034 study evaluating selinexor in combination with ruxolitinib in treatment naïve myelofibrosis to be presented at the 2022 ASH[1] meeting

- Compelling data published in ASH abstract reinforce continued development of the combination
- Received orphan drug designation for selinexor for the treatment of myelofibrosis in Europe[2]

MDS (Eltanexor) Completed enrollment for interim analysis in relapsed/refractory MDS Phase 2

- FDA Fast Track designation[3]
- Waiting for overall survival data maturity and expect to present data in 4Q 2022 / 1Q 2023

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1.American Society of Hematology
2. Received in October 2022
3.Received in July 2022 for the development of eltanexor as a monotherapy for the treatment of patients with relapsed or refractory intermediate, high-, or very high-risk MDS per IPSS-R

Sohanya Cheng
Chief Commercial Officer

COMMERCIAL HIGHLIGHTS

XPOVIO Update: 3Q 2022

Net Product Revenue up 20% YoY Driven by Growth in 2L-4L

3Q 2022 Highlights

- Net product revenue up 20% for 3Q22 vs 3Q21
- Increasing use of XPOVIO in earlier lines; fastest growing brand in 3L multiple myeloma in 1H 2022[1]
- Growth in both new patient starts and refills
- Strong double-digit growth in Community, while Academic business remained stable despite increasing competition in late lines
- Continued improvement in perception and intent-to-prescribe data in 2-4L[2]

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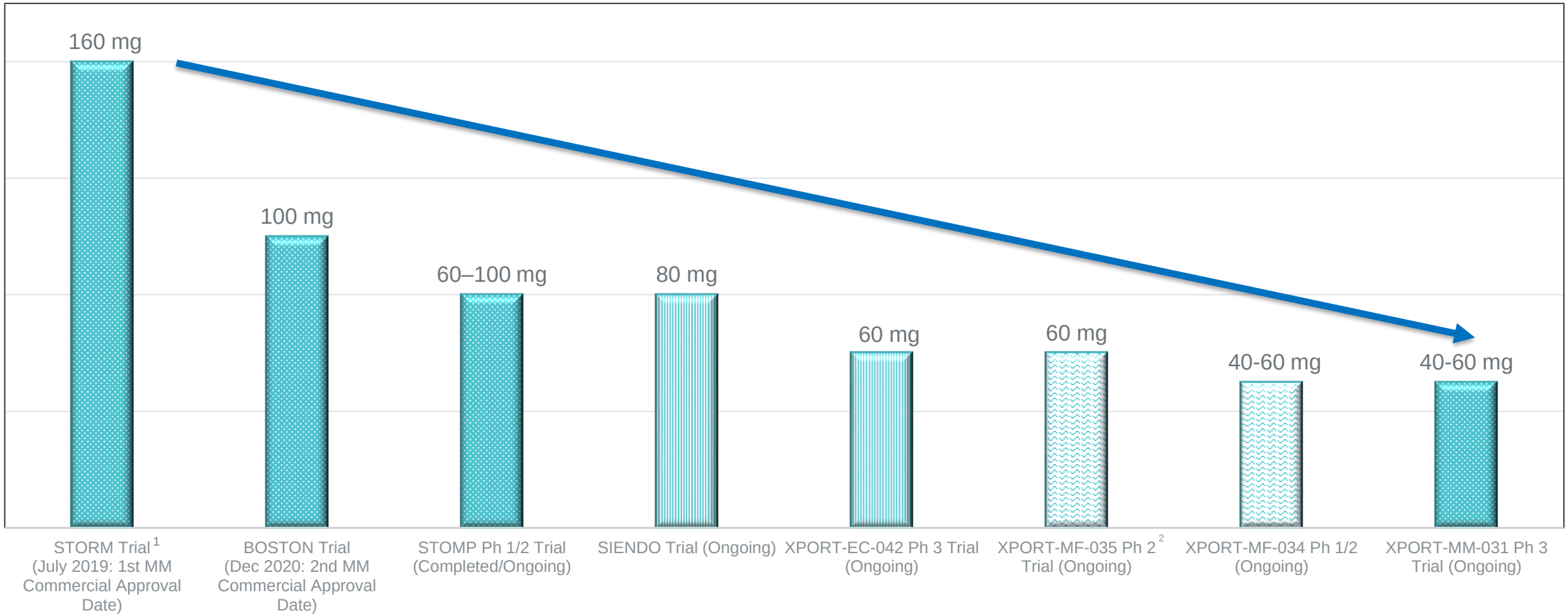
1. Assessed as of August 2022. Based on Komodo claims analysis, comparing U.S. XPOVIO market share in new patients vs other available brands approved in 3L MM in 2021 and 1H 2022
2. Based on internal KPTI Myeloma HCP ATU (healthcare professionals' awareness, trial and usage)

Reshma Rangwala, MD, PhD
Chief Medical Officer

PIPELINE UPDATE

Optimizing Selinexor Dose to Improve Patient Experience and Overall Benefit



1. 80mg bi-weekly selinexor approval with STORM data versus QW (weekly) selinexor in all other studies cited
2. Following 80mg weekly * 2 cycles

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Progressing Focused Pipeline 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	w/R-GDP	DLBCL (R/R)	XPORT-DLBCL-030[1]				
	monotherapy	Endometrial cancer (maintenance)	SIENDO				
	monotherapy	Endometrial cancer (maintenance; *TP53* wild-type)	XPORT-EC-042				
	w/pomalidomide + dexamethasone	Multiple myeloma (2L+)	XPORT-MM-031[2,3]				
	w/multiple approved agents	Multiple myeloma (relapsed/refractory)	STOMP[4]				
	monotherapy	Myelofibrosis (previously treated)	XPORT-MF-035				
	w/ruxolitinib	Myelofibrosis (treatment naïve)	XPORT-MF-034[5]				
ELTANEXOR	monotherapy	Myelodysplastic syndromes (refractory)	KCP-8602-801				

hematologic cancer solid tumor cancer Coming soon

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1. XPORT-DLBCL-030 is a Phase 2/3. 2. Versus elotuzumab, pomalidomide, and dexamethasone. 3. Sponsored by European Myeloma Network. 4. STOMP has a total of 11 arms; 1 arm still enrolling, 7 arms with patients still in follow up, 3 arms closed. 5. XPORT-MF-034 is a Phase 1/2.

Endometrial Cancer is the Most Common Gynecologic Cancer with Significant Unmet Need for Patients with Advanced or Recurrent Disease

What is Endometrial Cancer?

- Arises from the endometrium, the layer of cells that form the lining of the uterus.

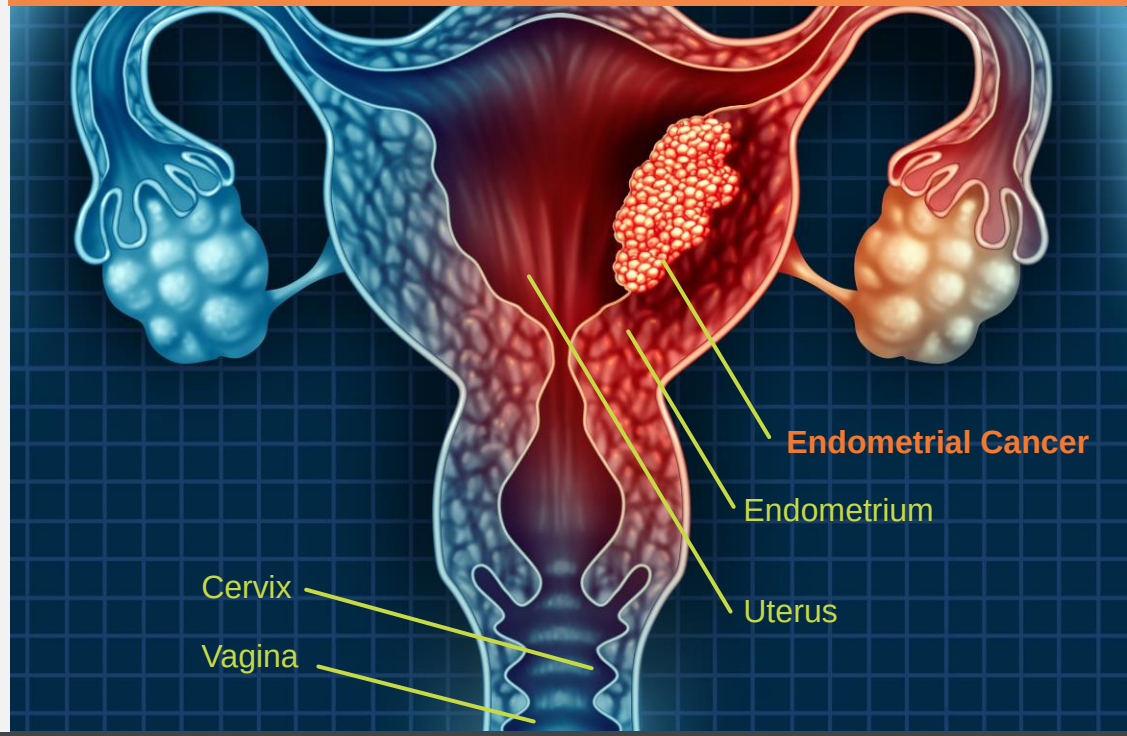
Treatment Landscape

- First-line treatment is chemotherapy (taxane plus platinum), where response rates can be as high as 67%[3]
- Following chemotherapy, NCCN Guidelines® recommend “watch and wait” until disease relapses[4]
- ~50% of patients with advanced or recurrent disease have *TP53* wild-type tumors[5]

Unmet Need

- Prognosis is poor, with **progression expected within ~4 months[6]** for patients responding to first-line chemotherapy treatment

There will be nearly 66,000 new and 14,000 advanced cases diagnosed in the U.S. in 2022[1] and more than 130,000 cases in Europe[2]



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.

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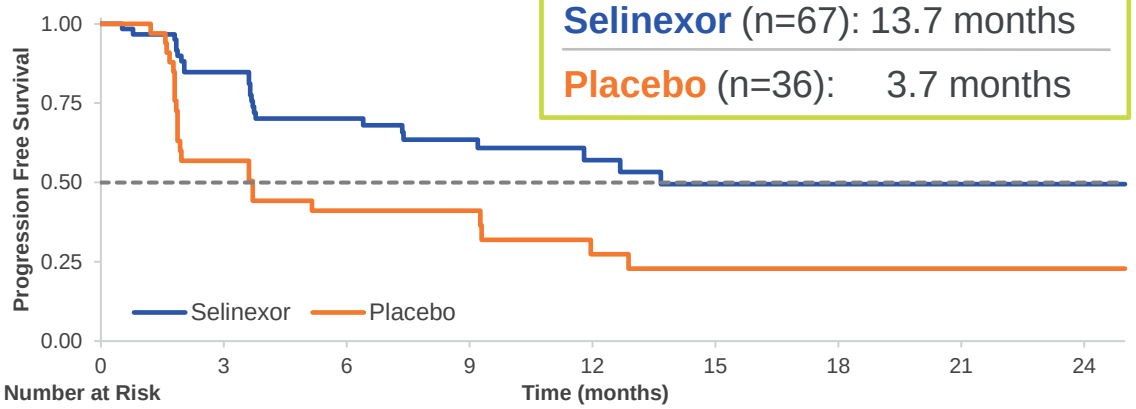
1. American Cancer Society, “About and Key Statistics.” Endometrial Cancer. https://www.cancer.org/content/dam/CRC/PDF/Public/8609.00.pdf ; Clarivate/DRG Endometrial Carcinoma Epidemiology Dashboard (2022 figures, pub 2020) 2. International Agency for Research on Cancer, World Health Organization. “Corpus uteri Fact Sheet.” Cancer Today, 2020. https://gco.iarc.fr/today/data/factsheets/cancers/24-Corpus-uteri-fact-sheet.pdf 3. Sorbe, B et al. Int J Gynecol Cancer. 2008). 4. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Uterine Neoplasms. v4.2021. September 3, 2021; www.nccn.org. 5. “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 6. Based on progression after 6 cycles of CP; Lorusso D. et al, 2015 by American Society of Clinical Oncology

TP53 Wild-Type has the Potential to be a Robust Biomarker in Endometrial Cancer

Supportive exploratory sub-group analysis from SIENDO trial: patients with stage IV or first relapse following chemotherapy for at least 12 weeks

Patients with *TP53* Wild-Type[1,2] Endometrial Cancer (n=103)

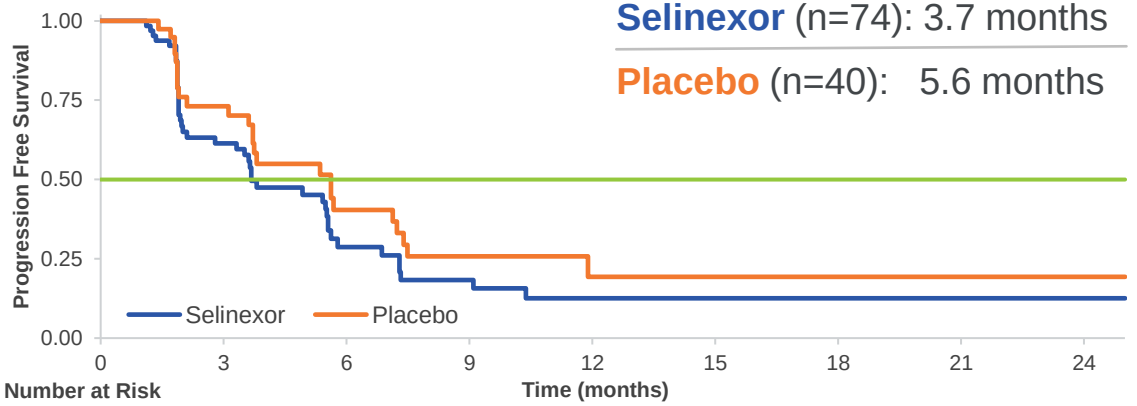
Median PFS
Selinexor (n=67): 13.7 months
Placebo (n=36): 3.7 months



Number at Risk									
Selinexor	67	48	33	24	15	10	7	5	1
Placebo	36	18	11	9	6	5	5	4	2

Patients with *TP53* Mutant [1,2] Endometrial Cancer (n=114)

Median PFS
Selinexor (n=74): 3.7 months
Placebo (n=40): 5.6 months



Number at Risk									
Selinexor	74	33	11	7	3	1	0	0	0
Placebo	40	25	11	7	3	3	3	2	2

SIENDO Trial adverse events (AEs) were generally manageable with supportive care and dose modifications. Most common Gr ≥3 treatment related AEs were neutropenia (14%) and fatigue (9%).

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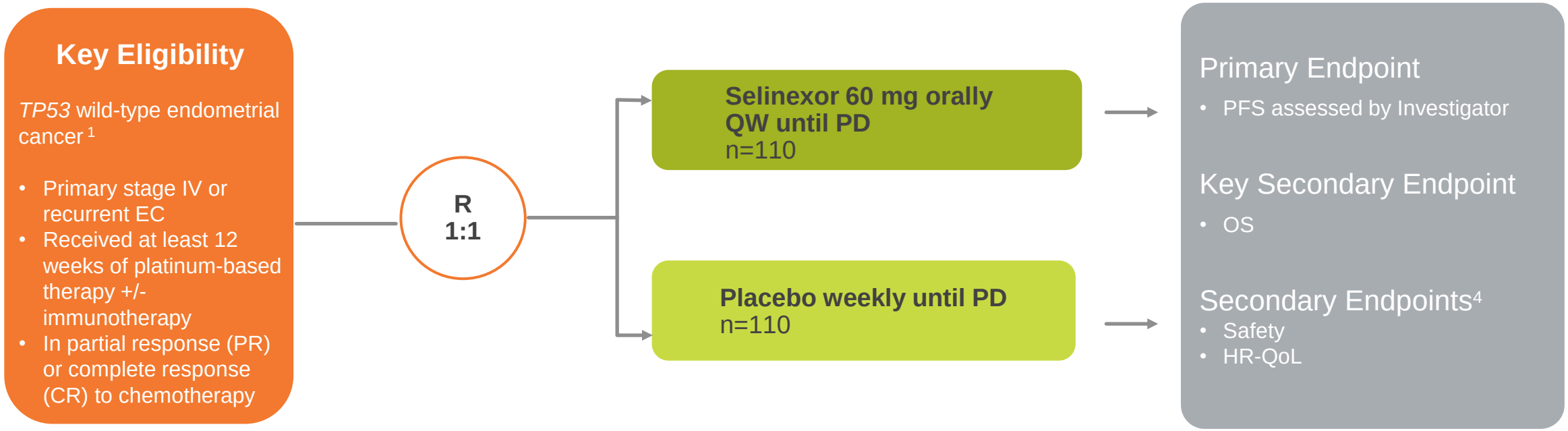
1. TP53 WT/MUT status of patients under continued evaluation. 20% of patients on the selinexor arm and 15% of patients on the control arm have pending tumor TP53 status. **2.** Preliminary data from pre-specified exploratory subgroup analysis as of the database lock date of January 18, 2022.

Initiated Global Phase 3 Registrational Study; *TP53* Mutation Status Will Be Assessed by Foundation Medicine[1]

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 ENGOT[2] and GOG[3]



- 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

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Selinexor Has the Potential to Improve Patient Outcomes in Myelofibrosis

What is Myelofibrosis (MF)?

- Bone marrow cancer that disrupts body's normal production of blood cells
- Causes extensive scarring in bone marrow, leading to enlarged spleen, severe anemia and constitutional symptoms

Treatment Landscape and Unmet Need

- Ruxolitinib is the standard of care for newly diagnosed MF
  - Approximately **40% of patients respond**[2]
  - Responses last up to 4 years
  - Once patients stop responding, the median survival is **only ~14 months**[3] and 5-year survival is ~ 18%[4]
  - In relapsed/refractory patients, an average of ~15%[5] (range <5-30%) of patients will achieve spleen volume reduction ≥ 35% (SVR35) with available therapies
- **No other approved class of therapies** other than JAK inhibitors in ~ 10 years

There are ~17,000 Americans living with MF in the U.S. each year[1]

JAK inhibitors are effective in the treatment of MF, but there are significant limitations

✓ **Decrease size of spleen**	✗ Worsening of pre-existing anemia and low platelets
✓ **Improve constitutional symptoms**	✗ Response can be transient or sub-optimal
✓ **Improve QoL**	✗ Limited effect on biology and natural history of the disease

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.

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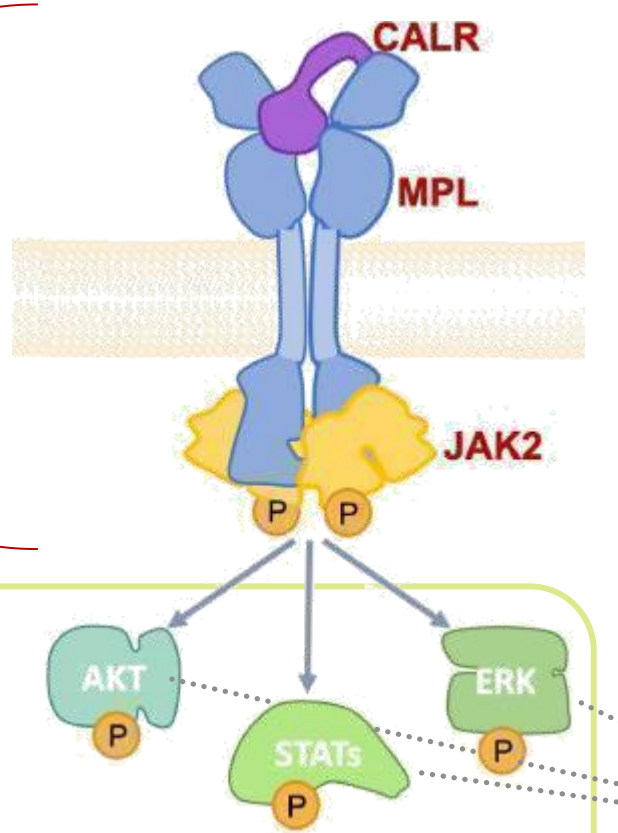
1. Clarivate/DRG Epidemiology Data (2022 figures, pub 2019). **2.** https://www.jakafi.com/myelofibrosis/high-risk-treatment. Accessed Nov 2021. **3.** Newberry KJ , et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. Blood . 2017;130:1125–1131; Palandri F, et al. Life after ruxolitinib: reasons for discontinuation, impact of disease phase, and outcomes in 218 patients with myelofibrosis. Cancer . 2019;26:1243–1252; Kuykendall AT, et al. Between a rux and a hard place: evaluating salvage treatment and outcomes in myelofibrosis after ruxolitinib discontinuation. Ann Hematol. 2018;97:435–441. 4. Price et al. PLoS One. 2014;9(3):e902995 5. Internal assumption based on historical range of <5-30% in the literature; 30% SVR35 rate at EOC6 in patients treated with fedratinib and who received at least 3 months of prior ruxolitinib (JAKARTA-2 updated analysis, Harrison et al 2020. Am J Hematol)

Selinexor Can Inhibit Multiple Targets of the JAK/STAT Pathway, Enabling Independent Suppression of MF cells and Potentially Complementing the Function of JAKi's[1,2,3,4,5]

MF is driven by **upstream mutations** of *JAK2, CALR* or *MPL*

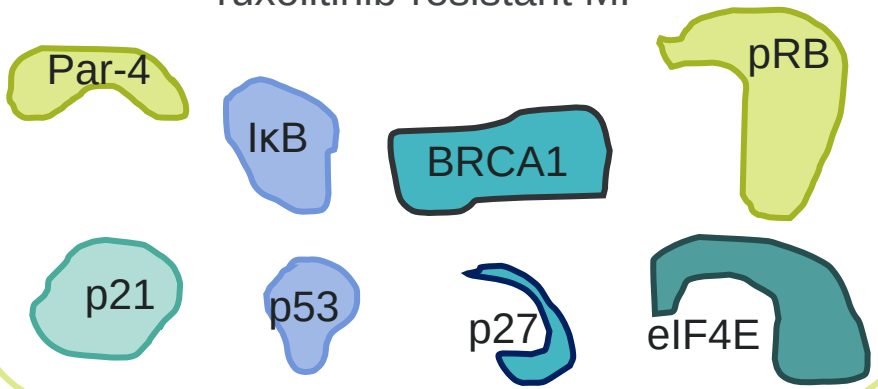


Downstream pathways are activated by the upstream mutations

The AKT, STAT and ERK pathways contain XPO1 cargo proteins

XPO1

Additional XPO1 cargos proteins that regulate cell growth and survival may be important, especially in ruxolitinib-resistant MF



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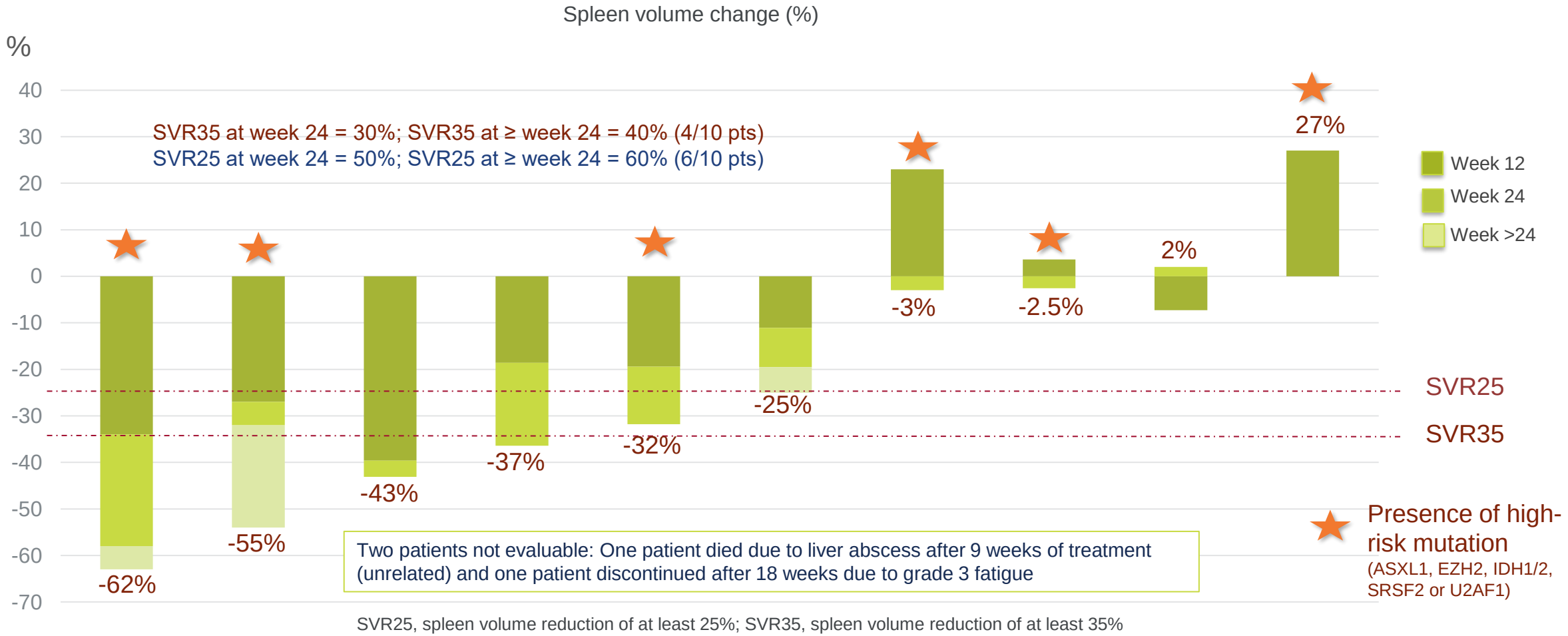
1. Exp Hematol (105):2-9, Jan. 01, 2022
2. XPO1 Cargo references: https://doi.org/10.7554/eLife.11466; http://prodata.swmed.edu/LRNes/IndexFiles/namesGood.php
3. Zhong et al., Leukemia. 2014 May;28(5):1158-63 ; 4. Muqbil et al., Cancer Lett. 2016 Dec 28;383(2):309-317
5. Cheng et al., Mol Cancer Ther. 2014;13(3):675-686

Single-Agent Selinexor Resulted in Sustained Spleen Responses in Refractory MF Patients in Phase 2 ESSENTIAL Study[1,2]



SVR25, spleen volume reduction of at least 25%; SVR35, spleen volume reduction of at least 35%

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.

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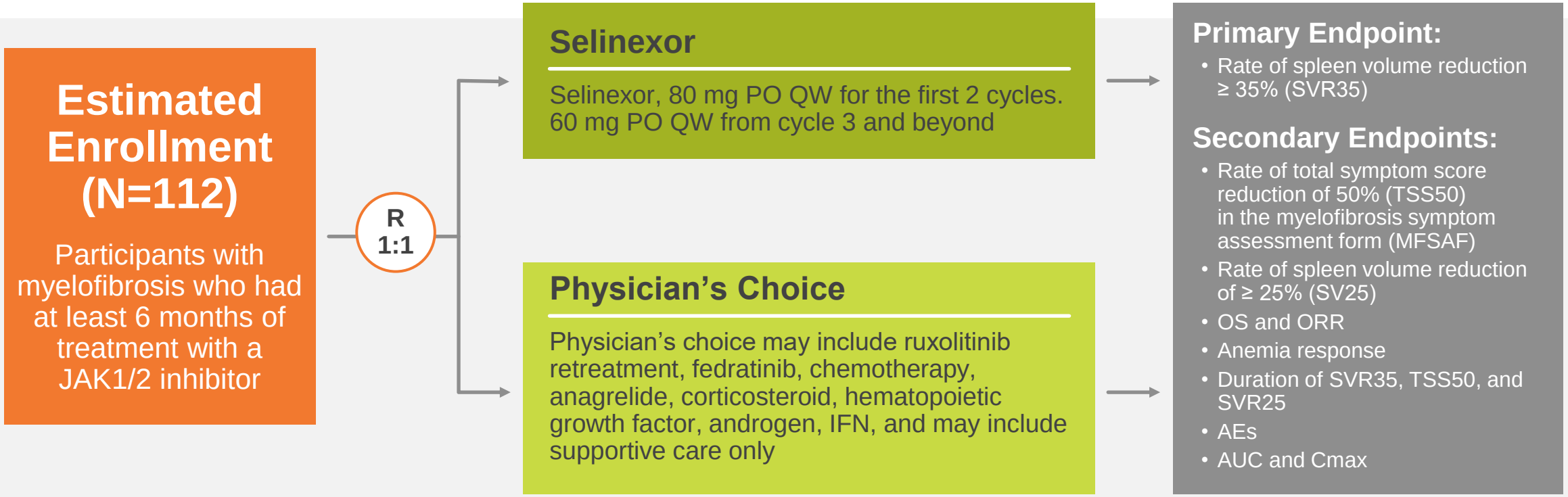
1. Tantravahi, et al. ASH 202 2. Data cut-off as of November 2021
2. Preliminary data cut from investigator sponsored open label trial

Phase 2 Study (XPORT-MF-035[1]) Evaluating Single-Agent Selinexor Versus Physician's Choice in Previously Treated MF



Top-line data expected in 2H 2023

1. NCT04562870

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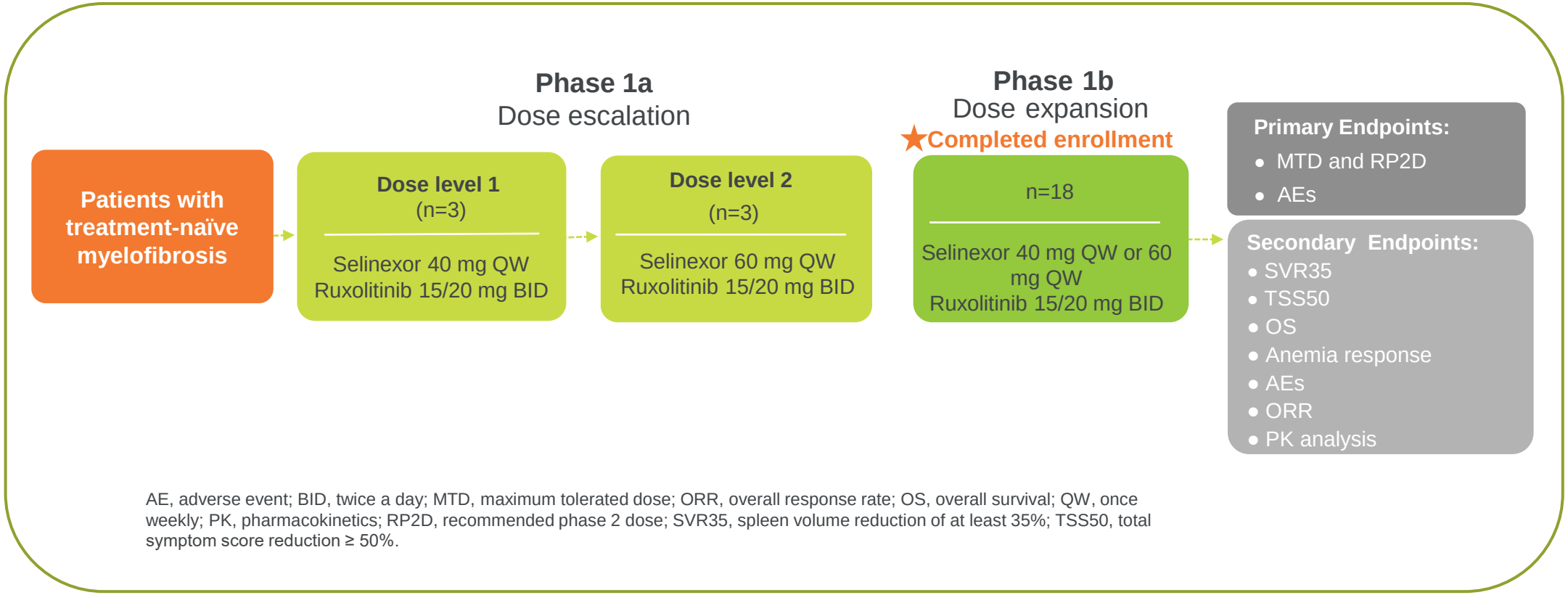
AEs, adverse events; AUC, area under the curve; Cmax, maximum concentration; ; IFN, interferon; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; QW, once weekly

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



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%.

1. NCT04562389

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Encouraging Preliminary Data[1,2] Across Key Efficacy Endpoints from Phase 1 Study (XPORT-MF-034); Updated Results To Be Presented at ASH 2022

SPLEEN RESPONSES AT 12 & 24 WEEKS

79% of evaluable patients[3] (11/14) achieved SVR35 at week 12

86% of evaluable patients[3] (6/7) achieved SVR35 at week 24

RAPID REDUCTION IN TOTAL SYMPTOM SCORES (TSS)

69% of evaluable patients[3] (9/13) achieved TSS50[4] at week 12

POSITIVE IMPACTS ON HEMOGLOBIN LEVELS

65% of patients[5] (11/17) maintained stable hemoglobin (± 2g/dL) or improved hemoglobin level (>2g/dL increase) at last follow up

SAFETY AND TOLERABILITY

Most common TEAEs[6] (n=19):
Nausea (58%), anemia (42%), vomiting (42%), majority Grade 1-2.
Most common Grade ≥ 3 TEAEs:
Thrombocytopenia (26%) and anemia (21%)

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

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1. Data cut from July 2022 2. ASH Abstract 2022 3. Efficacy evaluable at 12W: Patients who had a baseline efficacy evaluation and an on-treatment evaluation at 12 weeks; Efficacy evaluable at 24W: Patients who had a baseline efficacy evaluation and an on-treatment evaluation at 24 weeks. 4. TSS50 24W data not available at the time of data submission to ASH 5. Data from 17 transfusion independent patients who had at least 8 weeks of treatment; one patient was transfusion dependent at baseline and not included in the denominator 6. Treatment emergent adverse events

MICHAEL MASON
Chief Financial Officer

FINANCIAL RESULTS AND GUIDANCE

3Q 2022 Financial Results

Statements of Operations (millions)	3Q 2022	3Q 2021
Total Revenue	**$36.1**	**$37.7**
XPOVIO Net Product Revenue	32.0	26.7
License and Other Revenue	4.1	11.0
Total Operating Expenses[1]	**$67.0**	**$81.5**
Cost of Sales	1.0	0.6
Research and Development Expenses	31.4	45.8
Selling, General & Administrative Expenses	34.6	35.1
Net Loss	**$36.3**	**$51.8**
Net Loss per share	**$(0.45)**	**$(0.69)**

Balance Sheet (millions)	September 30, 2022	Dec 31, 2021
Cash, Cash Equivalents, Restricted Cash and Investments	**$150.1**	**$235.6**

2022 Financial Guidance

- Total Revenue of $155-$165 million
- Net Product Revenue of $120-$130 million, reflecting ~27% growth compared to 2021
- Non-GAAP R&D and SG&A Expenses of $250-$265 million[2]
  - Cost reduction initiatives aligned with prioritization of core programs reflected in R&D expenses in 2H 2022
- Cash runway expected to be sufficient to fund planned operations into early 2024

1. Total stock-based compensation expense $6.8million in 3Q 2022
2. Karyopharm has not reconciled the full year 2022 outlook for non-GAAP R&D and SG&A expenses to full year 2022 outlook for GAAP R&D and SG&A expenses because Karyopharm cannot reliably predict without unreasonable efforts the timing or amount of the factors that substantially contribute to the projection of stock compensation expense, which is excluded from the full year 2022 outlook for non-GAAP R&D and SG&A expenses

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Richard Paulson
Chief Executive Officer

CLOSING REMARKS

Upcoming Milestones for 2022 and Beyond

- Leverage commercial capabilities and increase U.S. XPOVIO sales (2022)
- Dose first patient in Phase 3 study evaluating selinexor + pomalidomide + dex (1H 2022) ✓
- EMA decision in 2L+ based on BOSTON study (2H 2022) ✓

- Report subgroup and molecular analysis data from SIENDO (ASCO 2022) ✓
- Initiate new registration-enabling Phase 3 study in *TP53* wild-type (2H 2022) ✓
- Report top-line results (2024)

- Report updated results from Phase 1 trial in combination with JAKi in treatment naïve MF (2H 2022)
- Report top-line Phase 2 selinexor data in previously treated MF (2H 2023)

- Report interim Phase 2 eltanexor data in relapsed/refractory MDS (4Q 2022 / 1Q 2023) and top-line data (2023)

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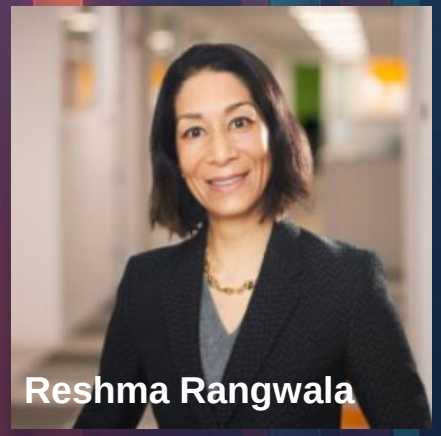
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