Karyopharm® Therapeutics

Second Quarter 2022 Financial Results & Business Update

August 4, 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, 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 March 31, 2022, which was filed with the Securities and Exchange Commission (SEC) on May 5, 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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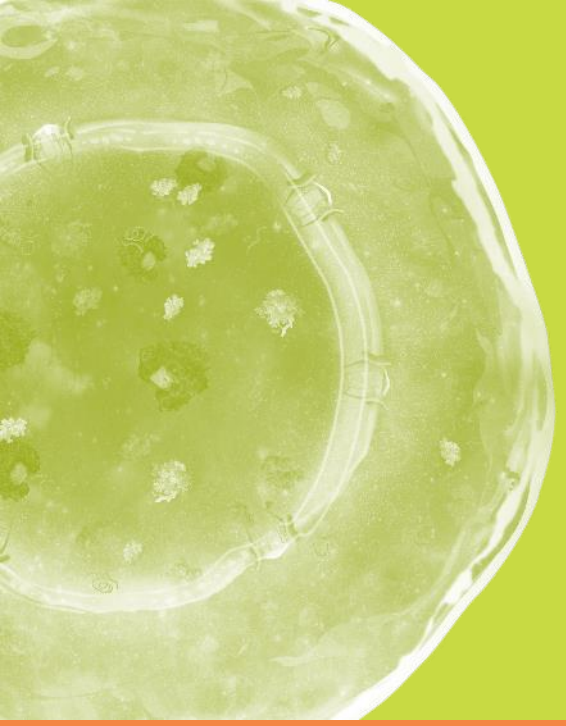
Richard Paulson
Chief Executive Officer

OVERVIEW



Leveraging the **inhibition of nuclear export** as a mechanism to treat cancer

Karyopharm® Therapeutics

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

Expanding on multiple myeloma foundation

Continued expansion of XPOVIO by driving commercial excellence, moving into earlier lines and global approvals

Focused mid- and late-stage clinical pipeline

Multiple catalysts expected near and mid-term, including pursuing approvals in endometrial cancer, myelofibrosis and myelodysplastic syndromes

Strong executive leadership

Strengthened leadership team with key appointments in 2022

Well-capitalized

Cash runway into early 2024

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Second Quarter 2022 and Recent Highlights

Strong Financials with Increasing Revenues and Cost Savings in 2022

2Q22 Total Revenue

$39.7M; 76% YoY growth

- Expanding global approvals driving growing levels of license and other revenue
- Cost management to match a focused pipeline

Expanding on Multiple Myeloma Foundation Globally

2Q22 Net Product Revenue

$29.0M; 44% YoY growth

- Full EU approval for NEXPOVIO expanding indication to 2L+
- Launches in mainland China by Antengene and Canada by Forus

XPOVIO® NEXPOVIO®

Continue to Advance Clinical Pipeline in Core Indications

Selinexor in Myelofibrosis

- Orphan drug designation by FDA
- Completing enrollment in Phase 1/2 frontline study in **myelofibrosis** for interim analysis in 2H22; encouraging initial data from selinexor + ruxolitinib combo presented at ASCO 2022

Eltanexor in MDS

- FDA Fast Track designation[1] and EU orphan drug designation
- Completed enrollment for interim analysis in relapsed refractory **MDS** Phase 2 study

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1. 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

Prioritized and Targeted Core Programs Focused on Driving Improved Patient Outcomes in Areas of High Unmet Need

MULTIPLE MYELOMA

Enabling **a 'Class Switch' in Earlier Lines of Therapy** to continue improving patient outcomes

ENDOMETRIAL CANCER

Potential to be the **First Maintenance-Only Treatment Option** for patients whose tumors are p53 wild-type

MYELOFIBROSIS

Potential to improve patient outcomes in **frontline and relapsed/refractory MF**

MYELODYSPLASTIC SYNDROMES

Potential to improve patient outcomes in **frontline and relapsed/refractory MDS**

Opportunity to expand into additional lines of therapy in all four core indications

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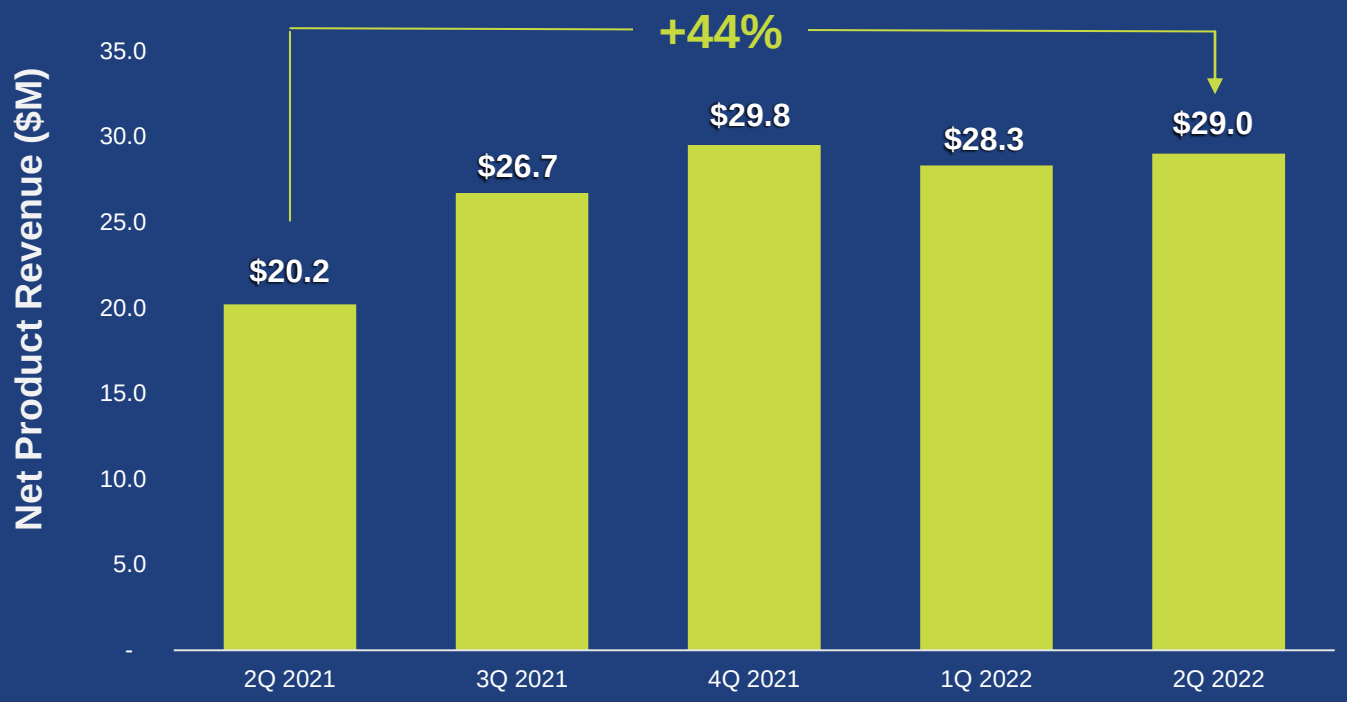
Sohanya Cheng
Chief Commercial Officer

COMMERCIAL HIGHLIGHTS

XPOVIO Launch Update: 2Q 2022

Net Product Revenue up 44% YoY Driven by Growth in 2L-4L



2Q 2022 Highlights

- Net product revenue up 44% for 2Q22 vs 2Q21
- Increasing use of XPOVIO in earlier lines; > 50% of patients in second to fourth lines[1]
- QoQ decline in refills, impacted by slow down of new patient starts (NRx) in January and February due to COVID-19, followed by NRx recovery in 2Q22.
- Continued strong growth in Community driven by positive shift in perception
  - Intensified competition in later lines in Academic centers
  - Future growth expected to come from increased penetration in Community setting and uptake in earlier lines

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1. Komodo Health Claims Data from June 2022

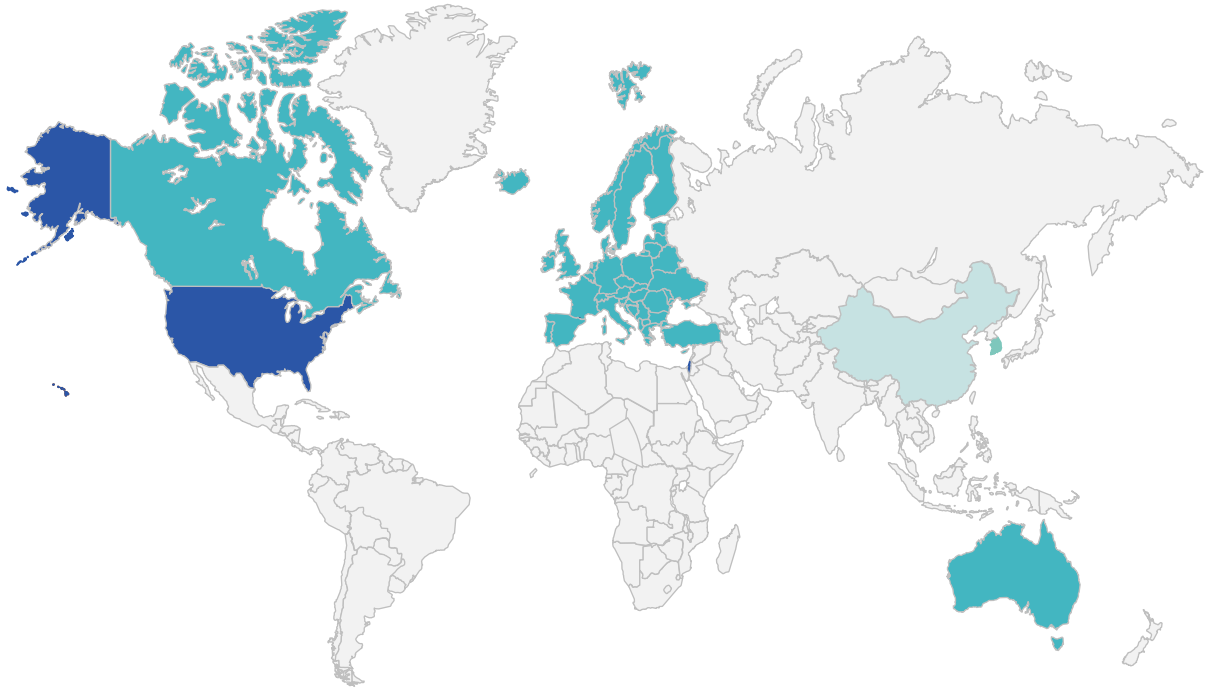
Reshma Rangwala, MD, PhD
Chief Medical Officer

PIPELINE UPDATE

Full EMA Approval Received for NEXPOVIO® Expanding Indication to 2L+

XPOVIO® / NEXPOVIO® Now Approved in 39 Countries

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
Hong Kong		Antengene



- 2L+ multiple myeloma and R/R DLBCL
- 2L+ multiple myeloma
- Penta- or triple-class-refractory multiple myeloma and R/R DLBCL
- Penta- or triple-class-refractory multiple myeloma

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1. The 27 countries comprising the European Union, plus Iceland, Norway, Northern Ireland and Lichtenstein.

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; p53 wild-type)					
	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				
	+ hypomethylating agents	Myelodysplastic syndromes (newly diagnosed)	KCP-8602-801				

hematologic cancer solid tumor cancer Coming soon

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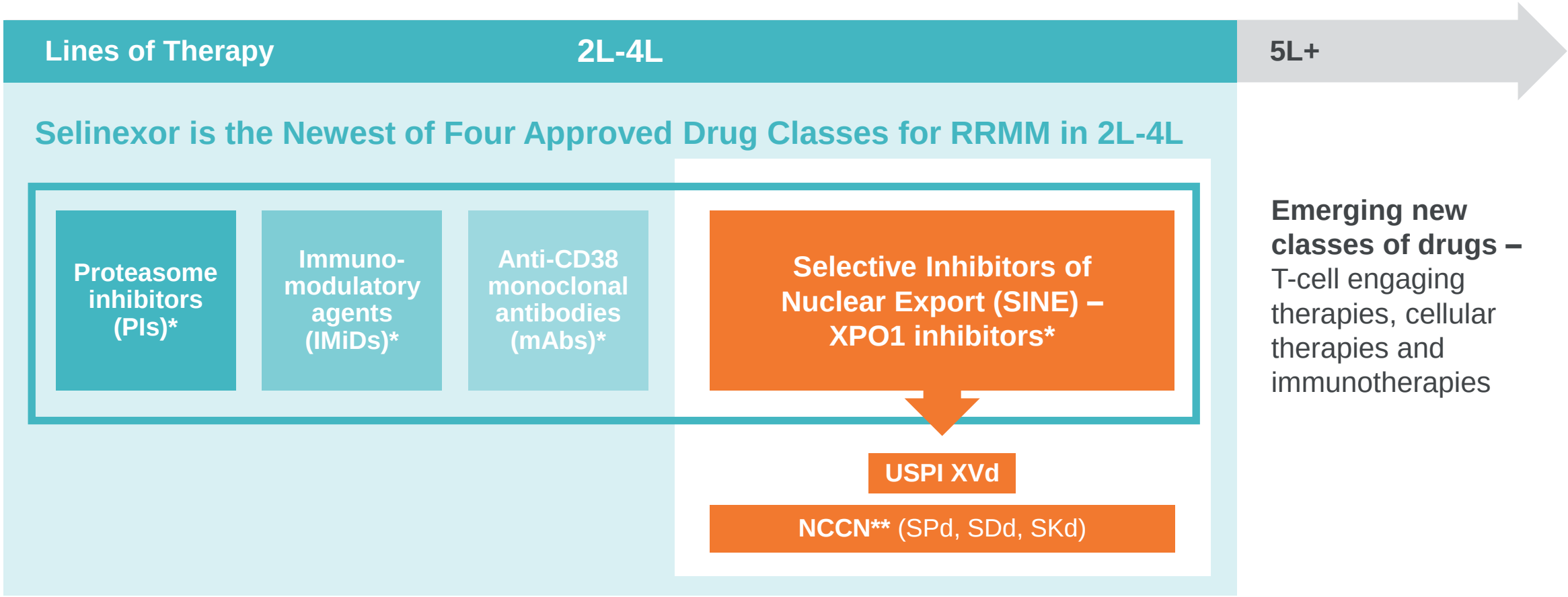
1. XPORT-DLBCL-030 is a Phase 2/3. 2. Versus elotuzumab, pomalidomide, and dexamethasone. 3. Sponsored by European Myeloma Network. 4. STOMP has a total of 11 arms; 1 arm still enrolling, 7 arms with patients still in follow up, 3 arms closed. **5.** XPORT-MF-034 is a Phase 1/2.

XPOVIO: 4th Novel Class of Therapy for 2L–4L RRMM post anti-CD38

XPOVIO Provides a Class Switch and Combinatorial Optionality to Future Regimens



Emerging new classes of drugs – T-cell engaging therapies, cellular therapies and immunotherapies

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

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

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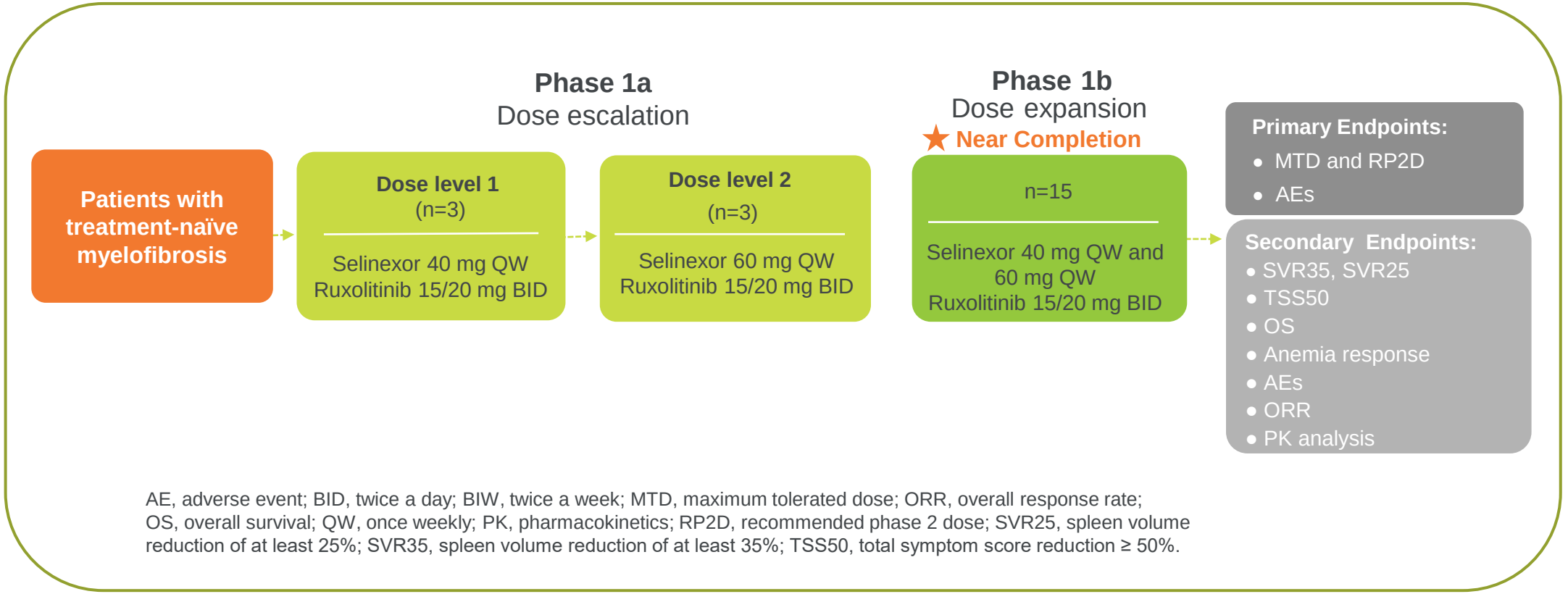
* +dexamethasone
** NCCN Guideline inclusion for SPd, SDd and SKd

Phase 1/2 Study (XPORT-MF-034[1]) Evaluating Selinexor in Combination with Ruxolitinib in Treatment-naïve Myelofibrosis



AE, adverse event; BID, twice a day; BIW, twice a week; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; QW, once weekly; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SVR25, spleen volume reduction of at least 25%; SVR35, spleen volume reduction of at least 35%; TSS50, total symptom score reduction ≥ 50%.

Preliminary Phase 1 Data Presented at ASCO 2022 and EHA 2022
Update from Phase 1 Expected in 2H 2022

1. NCT04562389

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

SPLEEN RESPONSES AT 12 WEEKS

75% of evaluable patients (6/8) achieved SVR35 at week 12

POSITIVE IMPACTS ON HEMOGLOBIN LEVELS

50% of patients (5/10) maintained stable hemoglobin (± 2g/dL) or improved hemoglobin level (>2g/dL increase) at last follow up

RAPID REDUCTION IN TOTAL SYMPTOM SCORES (TSS)

All evaluable patients (n=7) experienced improvements in symptom scores, with 3/7 patients achieving TSS50 at week 12

SAFETY AND TOLERABILITY

No dose limiting toxicities seen at either dose level

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.

1. Ali H, et al. Presented at: American Society for Clinical Oncology 2022 Annual Meeting; June 3-7, 2022. Abstract 7060.

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No Dose Limiting Toxicities Seen from Selinexor & Ruxolitinib Combination[1]

Treatment Emergent Adverse Events (TEAEs)

TEAEs[a]	Selinexor 40mg or 60mg PO QW + Ruxolitinib PO BID N=15		
Non-Hematologic, n (%)	**Grade 1**	**Grade 2**	**Grades 3 and 4[c]**
Nausea	4 (27)	1 (7)	1 (7)
Dysgeusia	3 (20)	1 (7)	-
Hyponatremia	3 (20)	-	-
Dizziness	3 (20)	-	-
Vomiting	2 (13)	1 (7)	-
Headache	1 (7)	2 (13)	-
Anorexia	1 (7)	-	1 (7)
Atrial Fibrillation	-	-	3 (20)
Failure to thrive[b]	-	-	1 (7)
Pulmonary hypertension	-	-	1 (7)
Tumor lysis syndrome	-	-	1 (7)
Hematologic, n (%)			
Neutropenia	2 (13)	-	3 (20)
Anemia	1 (7)	2 (13)	3 (20)
Thrombocytopenia	1 (7)	1 (7)	4 (27)

The combination of selinexor and ruxolitinib was generally well-tolerated:

- No dose limiting toxicities have been reported thus far at either dose level

Nausea was the most common TEAE

- 40% with majority Grade 1 events

Hematologic adverse events were reversible with dose interruptions and reductions

Dose reductions at last follow-up:

- Ruxolitinib dose reduced in 53% and selinexor dose reduced in 20% of patients

a. TEAEs Grades 1 and 2 that occurred in > 2 patients and TEAEs Grade ≥ 3 that occurred in at least 1 patient.
b. Serious adverse event of “failure to thrive” (related to study treatment) occurred at time of progression to AML and includes other Grade 3 adverse events deemed not related to selinexor or ruxolitinib: abdominal pain, atrial fibrillation, delirium, dysphagia, muscle weakness.
c. Majority of the TEAEs were Grade 3 except for one Grade 4 thrombocytopenia event.

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.

1. Ali H, et al. Presented at: American Society for Clinical Oncology 2022 Annual Meeting; June 3-7, 2022. Abstract 7060.

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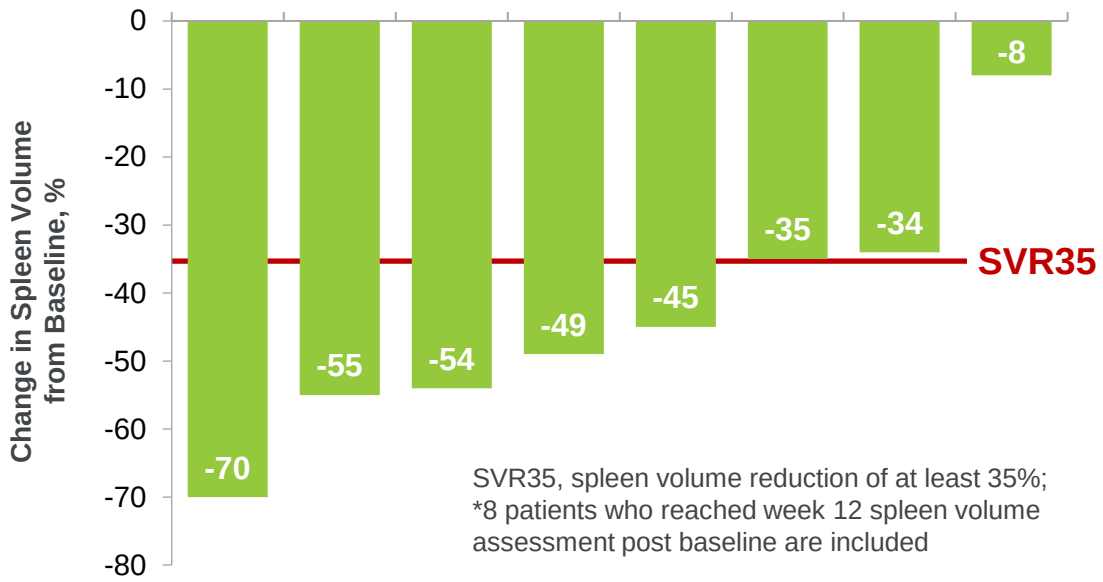
Selinexor & Ruxolitinib Combination Induced Rapid Spleen Responses and Reduction in Symptom Scores at Week 12[1]

Change in Spleen Volume from Baseline at 12 Weeks in All Evaluable Patients* (n=8)

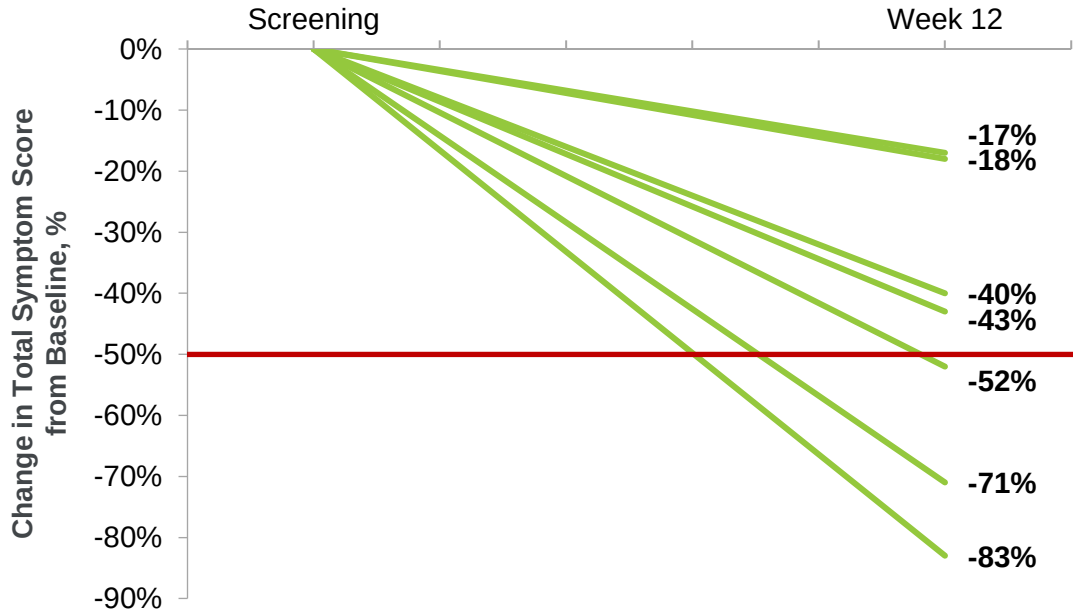


SVR35, spleen volume reduction of at least 35%;
*8 patients who reached week 12 spleen volume assessment post baseline are included

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.

75% (6/8) of Patients Had a ≥35% Reduction in Spleen Volume
on Treatment with Selinexor in Combination with Ruxolitinib at 12 weeks

Total Symptom Score at Week 12*



* 7 evaluable patients, who had been at least 12 weeks on treatment and had complete data; Scores from the Myelofibrosis Symptom Assessment Form were collected daily for 5–7 days prior to the start of each cycle. Median score was calculated for each cycle.

1. Ali H, et al. Presented at: American Society for Clinical Oncology 2022 Annual Meeting; June 3-7, 2022. Abstract 7060.

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Testing the Hypothesis that p53 Wild-Type has the Potential to be a Robust Biomarker in Endometrial Cancer

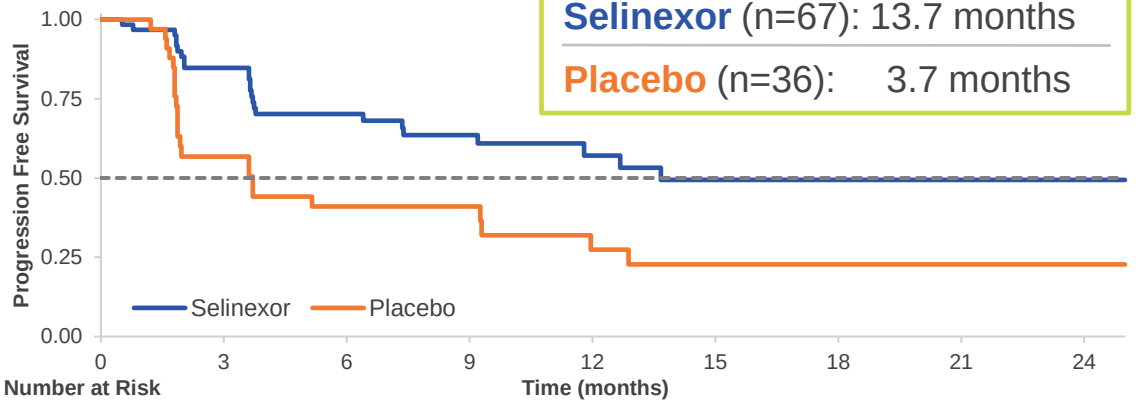
Supportive exploratory sub-group analysis from SIENDO trial: patients with Stage IV or first relapse following chemotherapy for at least 12 weeks

Patients with p53 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

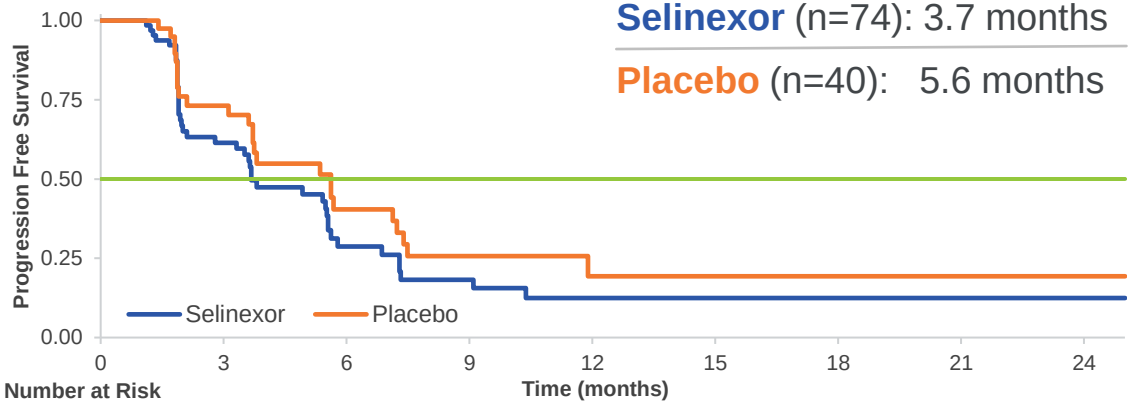
Selinexor	67	48	33	24	15	10	7	5	1
Placebo	36	18	11	9	6	5	5	4	2

Patients with p53 Mutant/Aberrant [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

Results from SIENDO Phase 3 evaluating selinexor in patients with advanced or recurrent endometrial cancer unlikely to support sNDA approval.
SIENDO Trial AEs were generally manageable with supportive care and dose modifications. Most common Gr ≥3 TRAEs were neutropenia (14%) and fatigue (9%).

Finalizing a CDx Partner Following Productive Dialogue with the FDA

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1. p53 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 p53 status. **2.** Preliminary data from pre-specified exploratory subgroup analysis as of the database lock date of January 18, 2022.

MICHAEL MASON
Chief Financial Officer

FINANCIAL RESULTS AND GUIDANCE

2Q 2022 Financial Results

Statements of Operations (millions)	2Q 2022	2Q 2021
Total Revenue	**$39.7**	**$22.6**
XPOVIO Net Product Revenue	29.0	20.2
License and Other Revenue	10.7	2.4
Total Operating Expenses[1]	**$82.6**	**$71.6**
Cost of Sales	0.9	1.1
Research and Development Expenses	44.3	34.0
Selling, General & Administrative Expenses	37.3	36.5
Net Loss	**$(49.1)**	**$(53.6)**
Net Loss per share	**$(0.62)**	**$(0.71)**

Balance Sheet (millions)	June 30, 2022	Dec 31, 2021
Cash, Cash Equivalents, Restricted Cash and Investments	**$172.6**	**$235.6**

Revised 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]
  - R&D expense in 2022 frontloaded due to clinical trial timing and severance charges
- Cash runway expected to be sufficient to fund planned operations into early 2024

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1. Total stock based compensation expense $15.1million in 2Q 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

Richard Paulson
Chief Executive Officer

CLOSING REMARKS

Upcoming Milestones for 2022 and Beyond

MULTIPLE MYELOMA

- Leverage commercial capabilities and increase US 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) ✓

ENDOMETRIAL CANCER

- Report subgroup and molecular analysis data from SIENDO (ASCO 2022) ✓
- Initiate new registration-enabling Phase 3 study in p53 wild-type (2H 2022)
- Report top-line results (2024)

MYELOFIBROSIS

- 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)

MYELODYSPLASTIC SYNDROMES

- Report interim Phase 2 eltanexor data in relapsed/refractory MDS (2H 2022) and top-line data (1H 2023)
- Report preliminary Phase 1 eltanexor data in combination with HMA in frontline MDS (2023)

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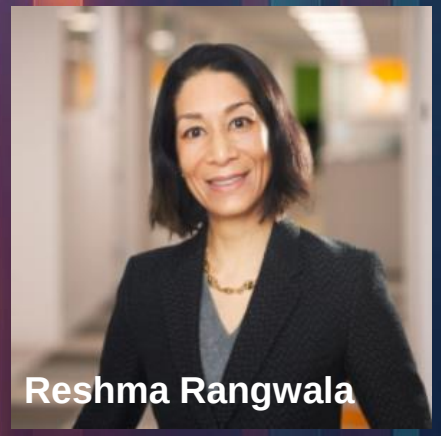
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