Karyopharm® Therapeutics

First Quarter 2022 Financial Results & Business Update

May 5, 2022

On Today's Call

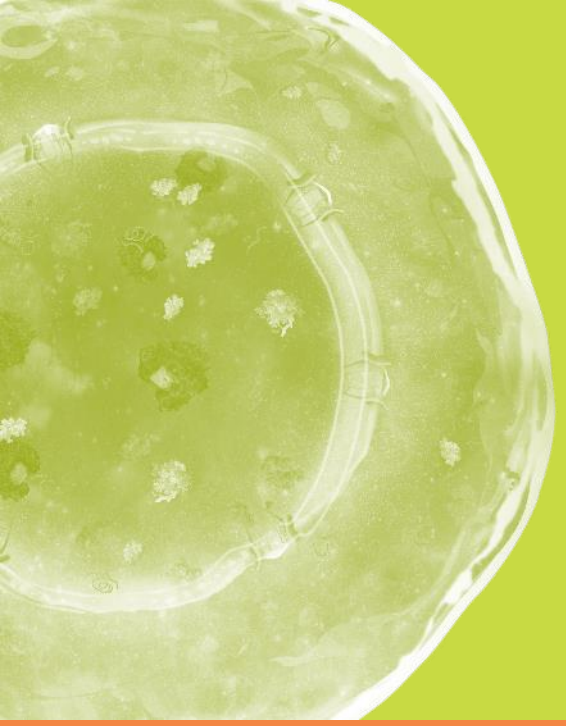
- **Welcome**
  Elhan Webb, *Senior Vice President, Investor Relations*
- **Overview**
  Richard Paulson, *President and Chief Executive Officer*
- **Commercial Highlights**
  Sohanya Cheng, *Chief Commercial Officer*
- **Pipeline Update**
  Dr. Reshma Rangwala*, Chief Medical Officer*
  Dr. Patricia Judson*, Senior Vice President, Medical Strategy*
- **Financial Summary and Guidance**
  Michael Mason, *Chief Financial Officer*
- **Closing Remarks**
  Richard Paulson, *President and Chief Executive Officer*
- **Q&A Session**

Forward-looking Statements and Other Important Information

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Karyopharm's guidance on its 2022 net product revenue and 2022 non-GAAP research and development and selling, general and administrative expenses; 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; that regulators will grant confirmatory approval in the European Union based on the BOSTON study in adult patients with multiple myeloma; 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 Annual Report on Form 10-K for the fiscal year ended December 31, 2021, which was filed with the Securities and Exchange Commission (SEC) on March 1, 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.

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 near and mid-term, pursuing approvals in endometrial cancer, myelofibrosis and myelodysplastic syndromes

Strong executive leadership

Strengthened leadership team with key appointments in Q1 22

Well-capitalized

Cash runway into early 2024

First Quarter 2022 and Recent Highlights

Expanding on multiple myeloma foundation

1Q22 total revenues

$47.7M

- 1Q22 net product revenue of $28.3M, 30% growth YoY

XPOVIO® NEXPOVIO®

Now approved in **37** countries

Focused mid- and late-stage clinical pipeline

Planning to initiate Ph3 study evaluating selinexor in p53 wild-type endometrial cancer in 2H22

- Promising exploratory subgroup data from the SIENDO study

2022 ASCO® ANNUAL MEETING

- Subgroup and molecular analysis from SIENDO study in **endometrial cancer**
- Preliminary data from Phase 1/2 study evaluating selinexor + ruxolitinib in frontline **myelofibrosis**

Strong executive leadership

New leadership team appointment

Reshma Rangwala, MD, PhD
Chief Medical Officer

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** with multiple combinations, to continue improving patient outcomes

~47,000 patients (2L+)[1,4]

ENDOMETRIAL CANCER

Potential to be the **First Maintenance Treatment** to improve patient outcomes versus "watch and wait"

~14,000 frontline[2,4] (~ 50% p53wt)

MYELOFIBROSIS

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

~5,800 frontline[6,4]

MYELODYSPLASTIC SYNDROMES

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

~15,000 intermediate-high risk frontline[3,4]

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

1. Clarivate/DRG Market Forecast Dashboard-MM(2022 figures, pub 2020) 2. Clarivate/DRG Endometrial Carcinoma Epidemiology Dashboard (2022 figures, pub 2020) 3. Clarivate/DRG Myelodysplastic-Syndrome-Epidemiology-Dashboard (2022 figures, pub 2020) 4. Annual U.S. incidence. 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. Epic Oncology Myelofibrosis((2022 figures, pub 2021))

Sohanya Cheng
Chief Commercial Officer

COMMERCIAL HIGHLIGHTS

XPOVIO Evolving Into a Standard of Care with Dose and Schedule Refined Over Time to Improve Efficacy and Patient Experience

From the STORM trial to the BOSTON trial to the STOMP trial, XPOVIO dosing has been continually refined to help optimize the patient experience

Approval Date: July 2019	Approval Date: Dec 2020	Ongoing/Completed
1st approval in MM Dose: **160 mg (80 mg twice weekly)**	2nd approval in MM Dose: **100 mg once weekly**	Phase 1/2 study in MM Dose range: **60-100 mg once weekly**
Xd STORM	**XVd** BOSTON	**SPd, SKd, SDd** STOMP
Phase 2b, single-arm, open-label, multicenter study Patients with penta-refractory MM	Phase 3, 2-arm, active comparator-controlled, open-label, multicenter study After at least 1 prior therapy in MM	Phase 1/2, open-label, multicenter study Patients with RRMM (dose escalation/expansion)

Once Weekly *(previously twice weekly)*

Lower Dose *(previously a higher dose)*

XPOVIO-based Triplets *(previously a doublet)*

Earlier Lines *(previously only in later lines)*

Supportive Care *(active symptom management)*

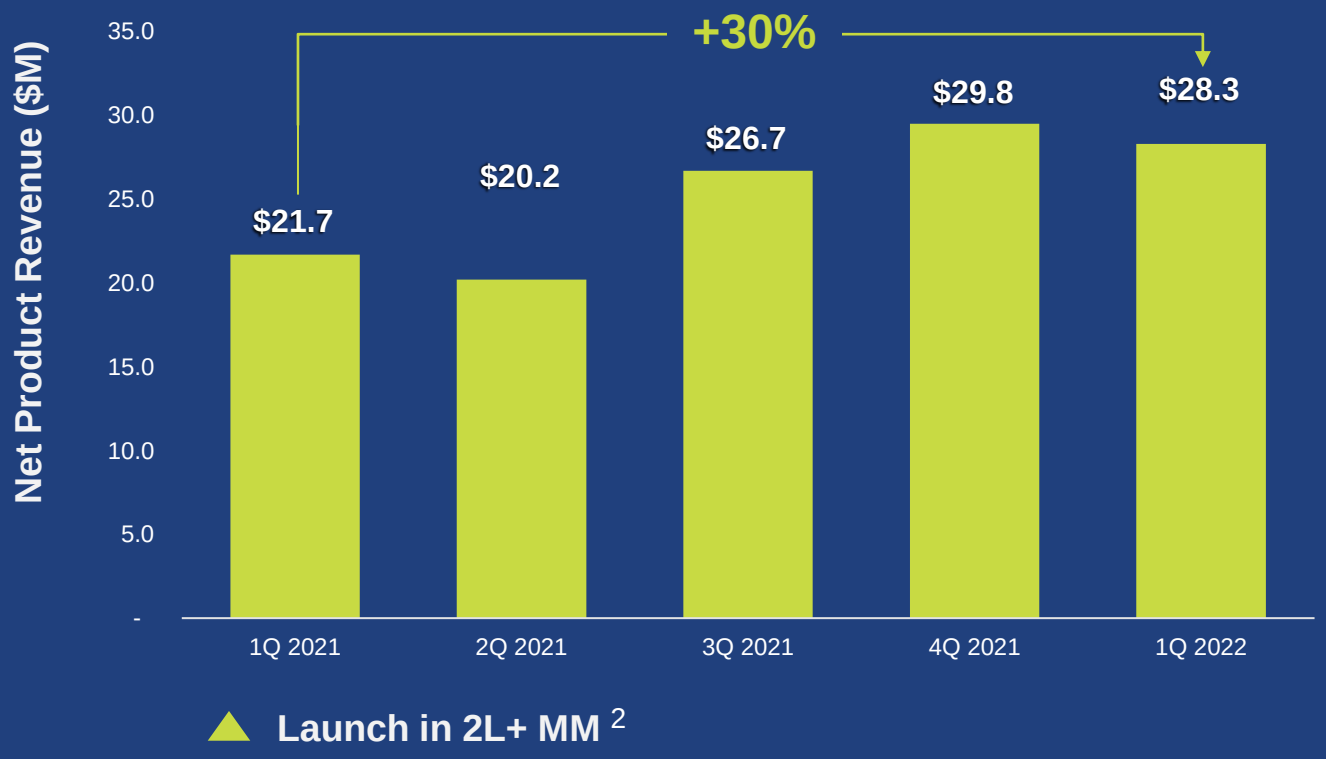
*STOMP was designed to study selinexor in combination with other MOAs across multiple triplet and quadruplet regimens, including XVd.
MM=multiple myeloma; MOA=mechanism of action; RRMM=relapsed or refractory multiple myeloma.

Combinations other than XVd and Xd are not promoted by Karyopharm, but may be considered for future indication updates

XPOVIO Launch Update: 1Q 2022

Sustained Growth in 2L-4L

Net Product Revenue **$28.3M** 1Q 2022



1Q 2022 Highlights

- Net product revenue up 30% for 1Q22 vs 1Q21
- Marketplace impacted by Omicron variant in January and February[1]
- Continued shift into earlier lines of therapy 2-4L[1] with strongest growth in 3L
- Continued increase in depth and breadth of use
- Continued positive shift in intent-to-prescribe metrics

1. Komodo Health Claims Data. 2. Approval of 2L+ MM in December 2020.

Reshma Rangwala, MD, PhD
Chief Medical Officer

Patricia Judson, MD
Senior Vice President, Medical Strategy

PIPELINE UPDATE

Progressing Focused Pipeline Across Cancers With High Unmet Needs

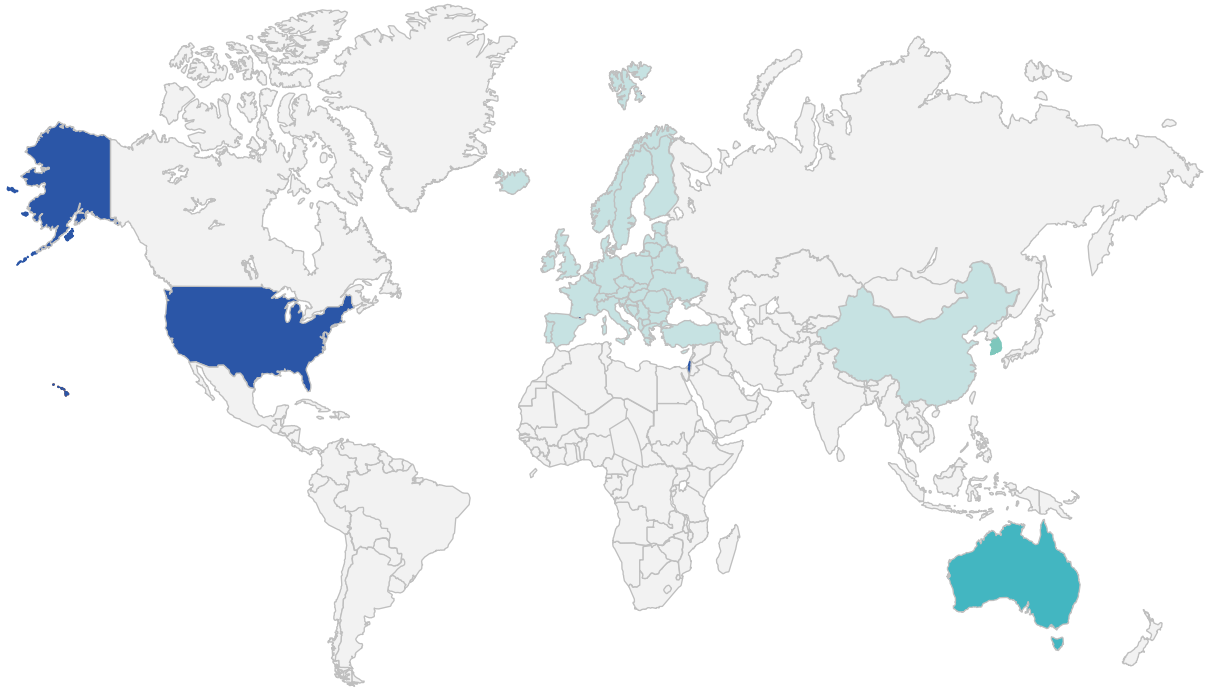
	Regimen	Indication	Study Name	Early Stage	Mid Stage	Late Stage	Commercial
XPOVIO (selinexor)	w/dexamethasone	Multiple myeloma (penta-refractory)	STORM				
	w/bortezomib + dexamethasone	Multiple myeloma (2L+)	BOSTON				
	monotherapy	DLBCL (R/R)	SADAL				
SELINEXOR	w/R-GDP	DLBCL (R/R)	XPORT-DLBCL-030[1]				
	monotherapy	Endometrial cancer (maintenance)	SIENDO				
	monotherapy	Endometrial cancer (maintenance; p53 wild-type)					
	w/pomalidomide + dexamethasone	Multiple myeloma (2L+)	XPORT-MM-031[2,3,4]				
	w/standard approved therapies[5]	Multiple myeloma (relapsed/refractory)	STOMP				
	monotherapy	Myelofibrosis (previously treated)	XPORT-MF-035				
	w/ruxolitinib	Myelofibrosis (treatment naïve)	XPORT-MF-034[6]				
ELTANEXOR	monotherapy	Myelodysplastic syndromes (refractory)	KCP-8602-801				
	+ hypomethylating agents	Myelodysplastic syndromes (newly diagnosed)	KCP-8602-801				

hematologic cancer solid tumor cancer Coming soon

1. XPORT-DLBCL-030 is a Phase 2/3. 2. Versus elotuzumab, pomalidomide, and dexamethasone.
3. Study expected to dose first patient in 1H22. 4. Sponsored by European Myeloma Network.
5. STOMP has a total of 11 arms; 1 arm still enrolling, 7 arms with patients still in follow up, 3 arms closed. **6.** XPORT-MF-034 is a Phase 1/2.

XPOVIO® / NEXPOVIO® Now Approved in 37 Countries

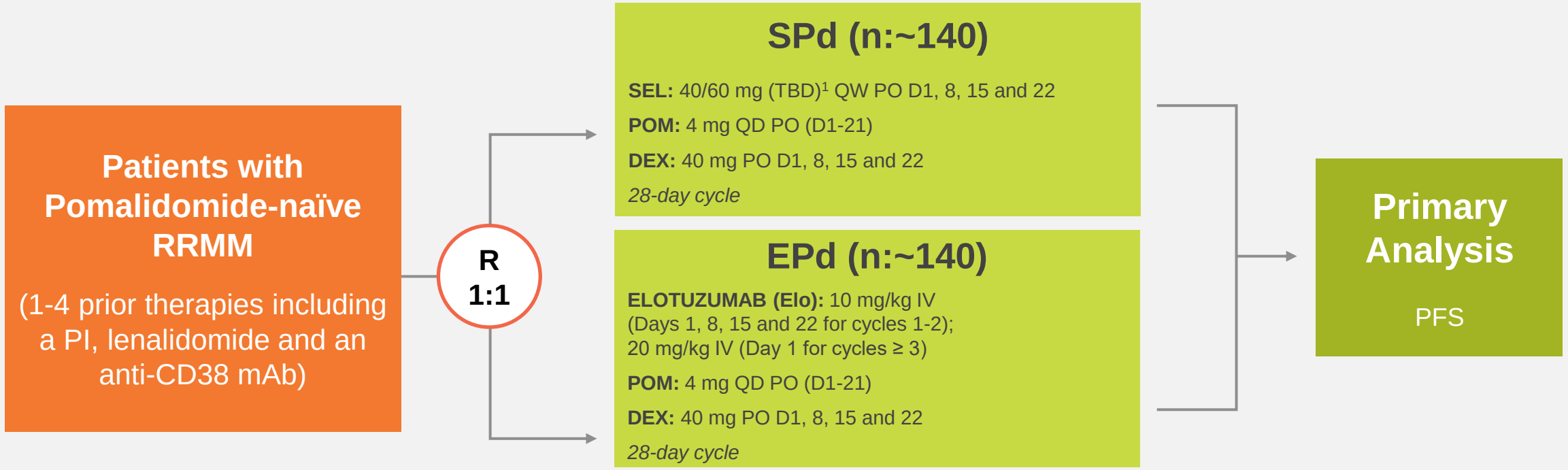
Country/Region	Indication(s)	Partner
Approvals		
United States		–
Europe[1]		Menarini
UK		Menarini
Mainland China		Antengene
South Korea		Antengene
Australia		Antengene
Singapore		Antengene
Israel		Neopharm
Pending Decisions		
Europe		Menarini
Canada		Forus Therapeutics
Taiwan		Antengene
Hong Kong		Antengene



- 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

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

Phase 3 Study (XPORT-MM-031) Evaluating Selinexor, Pomalidomide and Dexamethasone (SPd) in Patients with Previously Treated Multiple Myeloma



Expect to enroll first patient in 1H 2022

Top-line data expected 2024

1. Final dosing for Selinexor arm to be determined following interim analysis of data from first 60 patients

Significant Unmet Need for Patients with Advanced or Recurrent Endometrial Cancer

Endometrial cancer is the most common gynecologic cancer in the US[1]

Unlike other solid tumors, mortality continues to increase[2]

14,000 patients diagnosed with advanced or recurrent EC in the U.S. each year[3]

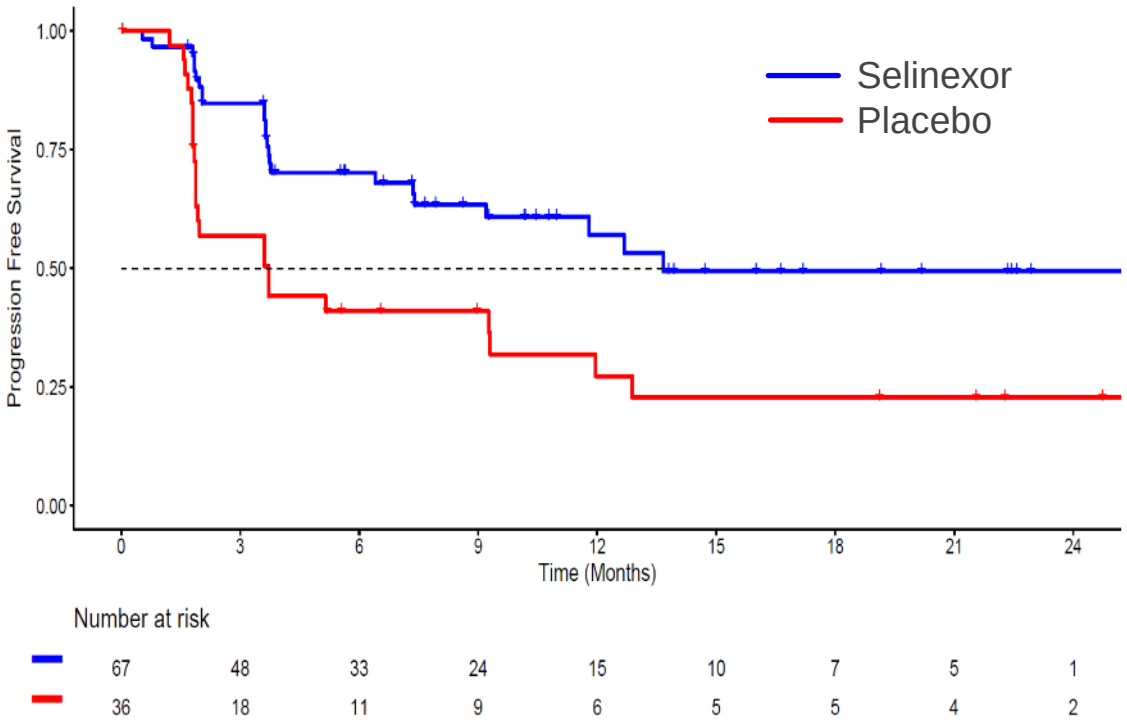
~50% of patients with advanced or recurrent EC have p53 wild-type tumors[4]

Standard of care is “watch-and-wait” following chemotherapy[5]

17% 5-year survival rate in advanced endometrial cancer[6]

1. www.hopkinsmedicine.org/health/conditions-and-diseases/endometrial-cancer. **2.** Siegel et al. 2021, 'Cancer Statistics, 2021', CA Cancer J Clin, 71: 7-33. **3.** Clarivate/DRG Epidemiology Data (2022 figures, pub 2020) 4. Cancer Genome Atlas Research et al. 2013, 'Integrated genomic characterization of endometrial carcinoma', Nature, 497: 67-73. **5.** National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Uterine Neoplasms. v4.2021. September 3, 2021; www.nccn.org. **6.** SEER. 2022. 'Cancer Stat Facts'.

PFS in Patients with p53[1,2] Wild-Type Endometrial Cancer



Patients with Stage IV or first relapse following chemo-therapy for at least 12 weeks

Median PFS[3]

Selinexor (n=67): 13.7 mo (95% CI 9.20-NR)

Placebo (n=36): 3.7 mo (95% CI 1.87-12.88)

IRT[4] HR = 0.407 (95% CI 0.229-0.724); one-sided p=0.0008[5] eCRF HR = 0.375 (95% CI 0.210-0.670); one-sided p=0.0003[5]

p-values are nominal and not adjusted for multiplicity

AEs were generally manageable with supportive care and dose modifications. Most common Gr ≥3 TRAEs were neutropenia (14%) and fatigue (9%).

Planning to initiate registrational-enabling study in 2H 2022

Top-line data expected in 1H 2024

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.** A pre-specified exploratory subgroup. 3. Preliminary data from pre-specified exploratory subgroup analysis as of the database lock date of January 18, 2022. 4. Unstratified p53wt data: HR = 0.426 (95% CI 0.240-0.756); one-sided p=0.0014. **5.** p-values are nominal and not adjusted for multiplicity.

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 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 US 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 US FDA or any other regulatory authority.

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)

Myelofibrosis Development

Targeting Relapsed/Refractory Population

Supportive Data from Phase 2 ESSENTIAL Study[1]

- Single-agent selinexor (60-80mg QW) in patients with myelofibrosis that is refractory or intolerant to JAK1/2 inhibitors

Durable spleen responses:

- 40% achieved SVR35 at ≥24W
- 60% achieved SVR25 at ≥24W
- 2-year survival probability: 92%

Positive impacts on hemoglobin levels:

- 50% of patients (4/8) achieved either improved hemoglobin levels or transfusion independence (TI)
- 40% of transfusion dependent (TD) patients (2/5) became TI
- Hemoglobin increased by 2g/dl in 67% of patients (2/3)

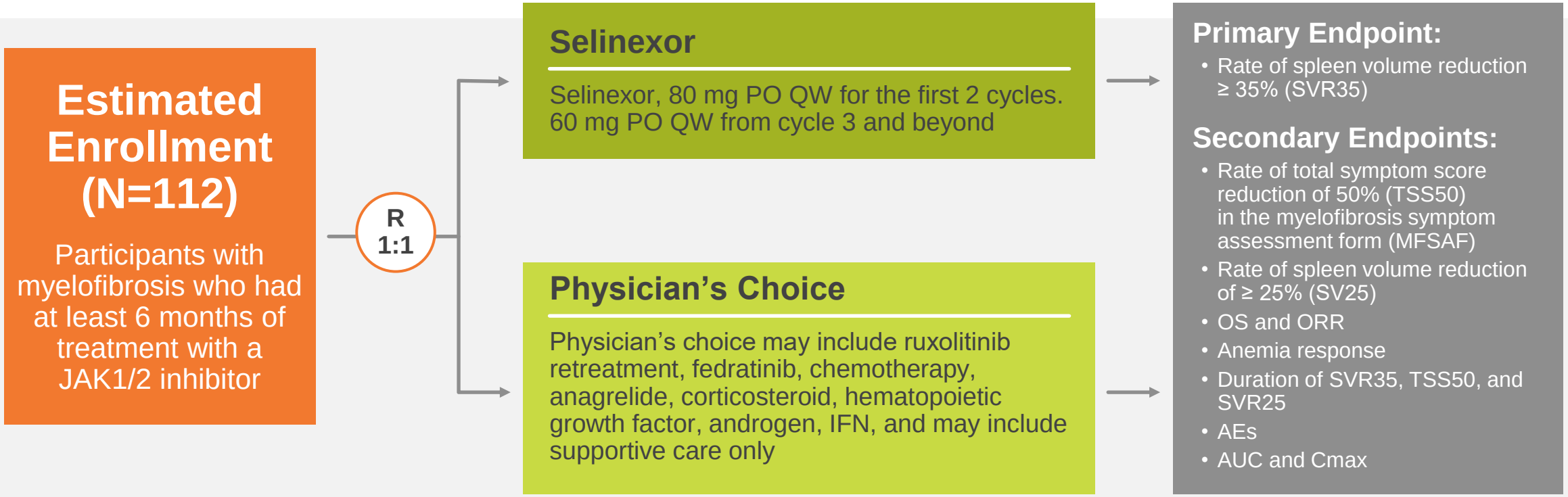
Tolerability and sustainability:

- Most common Gr ≥3 TRAEs: anemia (33%) and fatigue (33%)
- Median treatment duration: 11 months (range 2.8 to 28.8 months)

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. Tantravahi, et al. ASH 2021.

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



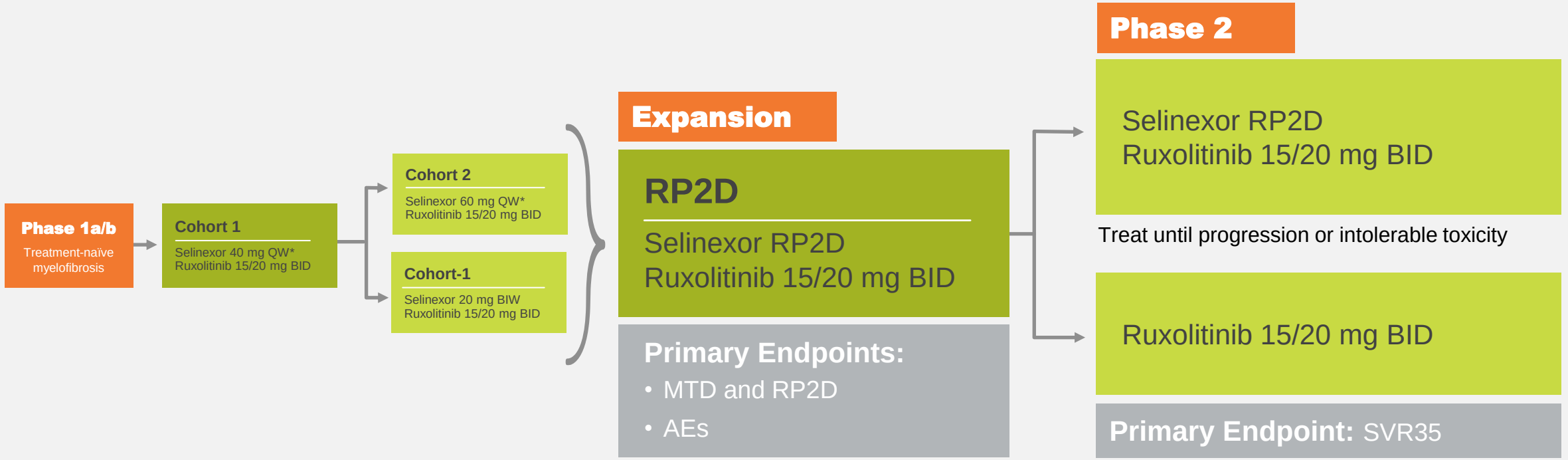
First patient dosed December 2021

Top-line data expected 2H 2023

1. NCT04562870

AEs, adverse events; AUC, area under the curve; Cmax, maximum concentration; DCR, disease control rate; DOR, duration of response; IFN, interferon; MDS, myelodysplastic syndrome; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; QW, once weekly;

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



Ph 2 Secondary Endpoints: Percentage of participants who will achieve TSS50 as measured by myeloproliferative neoplasm symptom assessment form, percentage of participants who will achieve SVR25, OS, anemia response, number of participants with AEs by occurrence, nature, and severity, duration of SVR35, duration of SVR25, duration of TSS50, ORR, Cmax, AUC

Preliminary Data From Phase 1 Selected for Presentation at ASCO 2022

1. NCT04562389

MICHAEL MASON
Chief Financial Officer

FINANCIAL RESULTS AND GUIDANCE

1Q 2022 Financial Results

Statements of Operations (millions)	1Q 2022	1Q 2021
Total Revenue	**$47.7**	**$23.3**
XPOVIO Net Sales	28.3	21.7
License and Other Revenue	19.4	1.5
Total Operating Expenses	**$82.3**	**$75.6**
Cost of Sales	1.4	0.9
Research and Development Expenses	42.1	37.1
Selling, General & Administrative Expenses	38.8	37.7
Net Loss	**$(41.4)**	**$(57.4)**
Net Loss per share	**$(0.53)**	**$(0.77)**

Balance Sheet (millions)	March 31, 2022	Dec 31, 2021
Cash, Cash Equivalents, Restricted Cash and Investments	**$207.0**	**$235.6**

2022 Financial Guidance

- Net Product Revenue of $135-$145 million, reflecting ~40% growth compared to 2021
- Non-GAAP R&D and SG&A Expenses of $265-$280 million[1]
- Cash runway expected to be sufficient to fund planned operations into early 2024

1. 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.

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)
- CHMP opinion in 2L+ based on BOSTON study[1] (1H 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 (1H 2024)

MYELOFIBROSIS

- Report preliminary Phase 1 data in combination with JAKi in treatment naïve MF (ASCO 2022)
- Report top-line Phase 2 selinexor data in previously treated MF (2H 2023)

MYELODYSPLASTIC SYNDROMES

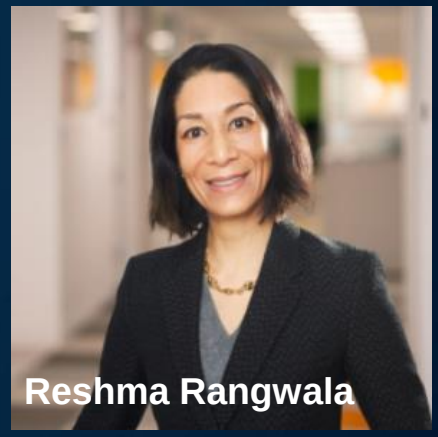
- Report preliminary Phase 1 eltanexor data in combination with HMA in frontline MDS (2H 2022)
- Report top-line Phase 2 eltanexor data in HMA-refractory MDS (1H 2023)

1. Approval of the BOSTON study will fulfill the Specific Obligation for the Conditional Marketing Authorization based on STORM

Q&A SESSION


Richard Paulson


Sohanya Cheng


Reshma Rangwala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Mike Mason