Karyopharm® Therapeutics

Investor Conference Call:

First Quarter 2021 Financial Results and Business Update

May 3, 2021

On Today's Call

Prepared Remarks

- **Michael G. Kauffman**, MD, PhD, *Co-Founder, Senior Clinical Advisor and Board Member*
- **Mike Mason**, MBA, *Chief Financial Officer*
- **Richard Paulson**, MBA, *President and Chief Executive Officer*

Joining for Q&A Session

- **John Demaree**, MBA**,** *Chief Commercial Officer*
- **Sharon Shacham,** PhD, MBA**,** *Chief Scientific Officer*
- **Stephen Mitchener***, PharmD, Chief Business Officer*
- **Ian Karp,** MBA, *Senior Vice President, Investor and Public Relations*

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 2021 non-GAAP research and development and selling, general and administrative expenses; expectations and plans relating to XPOVIO for the treatment of adult patients with relapsed or refractory multiple myeloma or relapsed or refractory diffuse large B-cell lymphoma; commercialization of XPOVIO or any of its drug candidates and the commercial performance of XPOVIO; submissions to, and the review and potential approval of selinexor 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 drug 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; 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, 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 year ended December 31, 2020, which was filed with the Securities and Exchange Commission (SEC) on February 24, 2021, 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.

Leadership Change a Natural Progression as Karyopharm is Increasingly Focused on Commercial Execution and Sales Expansion

- Richard Paulson appointed Karyopharm's next President and Chief Executive Officer
  - Member of Karyopharm Board of Directors since February 2020
  - Recent Chief Executive Officer of Ipsen North America and former Vice President and General Manager of Oncology at Amgen
  - Extensive commercial background and track record of success launching best-in-class products across multiple therapeutic areas including oncology medicines
- Dr. Michael Kauffman, co-founder and first CEO, to remain on Board of Directors and serve as Senior Clinical Advisor to help advance Karyopharm's broad clinical development pipeline with increasing focus on solid tumor indications
- Dr. Sharon Shacham, co-founder, to remain as Chief Scientific Officer

Q1 2021 and Recent Achievements Further Advance Karyopharm's Mission

Commercial Update

- Q1 2021 total revenues of **$23.3M** including XPOVIO® (selinexor) net sales of **$21.7M**
- XPOVIO prescription (RX) demand **increased 17%** in Q1 2021 as compared to Q4 2020 following expanded FDA indication granted in December 2020 (Approximately 1,170RXs vs. 1,000 RXs)
- **>160 new** physicians / accounts prescribed XPOVIO for the 1st time in Q1 2021

Pipeline / Clinical Data Update

- **Conditional Marketing Authorization** granted for NEXPOVIO® (selinexor) in Europe
- Type II Variation Marketing Authorization Application **validated by EMA** (based on Phase 3 BOSTON clinical data)
- **First set of data** from Phase 3 SEAL trial in advanced dedifferentiated liposarcoma published
- **1st patients dosed** in company-sponsored clinical study in DLBCL
- **16 abstracts selected** for presentation at 2021American Society of Clinical Oncology (ASCO) Annual Meeting

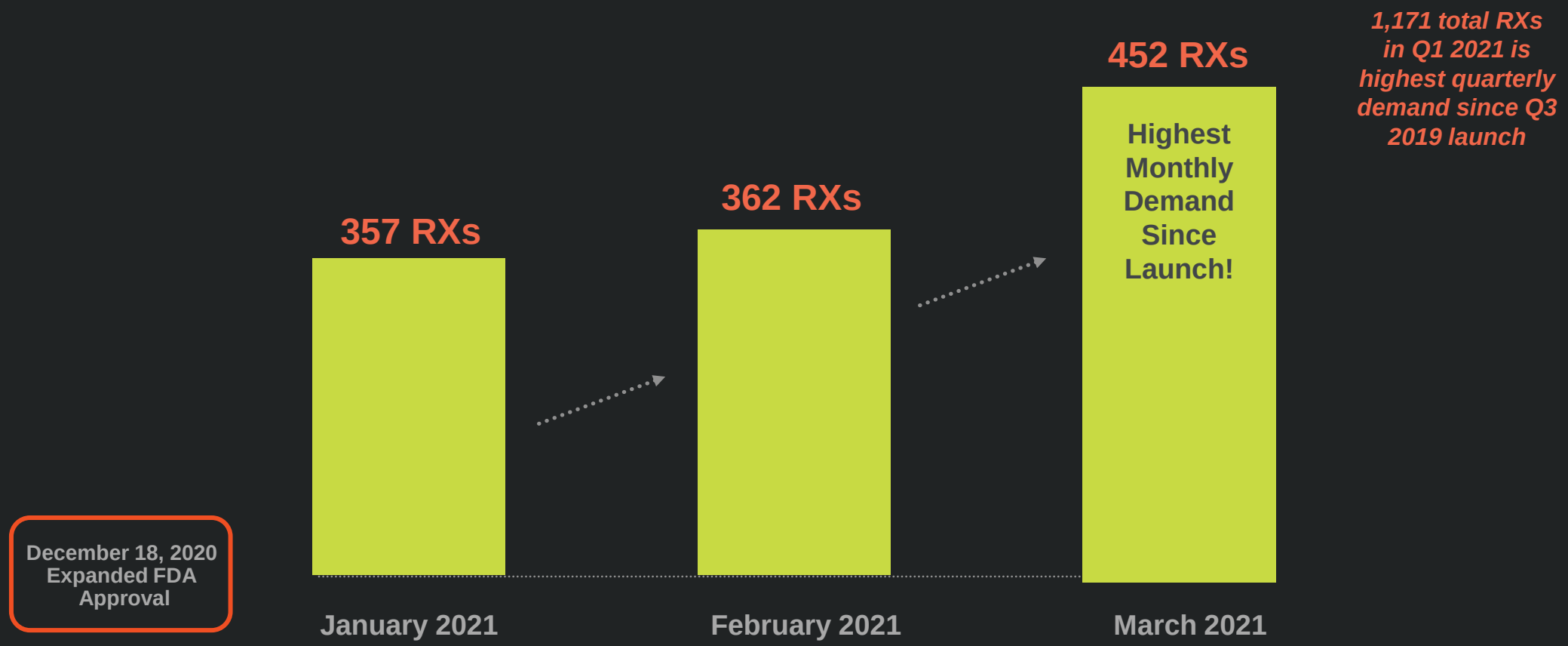
Corporate Development and Balance Sheet

- CEO transition announced; Richard Paulson appointed next Karyopharm President and CEO
- Ended Q1 2021 with **$233.6M** in cash, cash equivalents, restricted cash and investments
- Cash runway expected to be sufficient to fund planned operations into **late 2022**

Q1 2021 and Recent Sales Trends

- Q1 XPOVIO sales grew by 7% and RX demand increased by 17% compared to Q4 2020
  - Increase in RXs primarily driven by multiple myeloma new patient starts
  - Payer coverage for expanded indication has been strong with minimal on-label denials seen since launch
  - Higher gross-to-net discounts in Q1 2021 compared to Q4 2020 impacted sales growth
  - Inventory build at our distribution partners ahead of BOSTON launch was higher in Q4 2020 as compared to Q1 2021, which also impacted sales comparison, quarter-over-quarter
- We are encouraged to see patient demand for XPOVIO return to growth in the first quarter of 2021, and we remain confident in its long-term commercial potential and our ability to further increase utilization
- We expect to see benefit of longer duration of XPOVIO treatment based on “BOSTON” regimen to positively impact sales beginning in Q2 2021 but more likely increasing in the 2nd half of 2021
- We expect our field facing teams to have better access to customers in the 2nd half of 2021
- No new feedback or surprises regarding side effect profile of XPOVIO in the commercial setting following expanded FDA approval

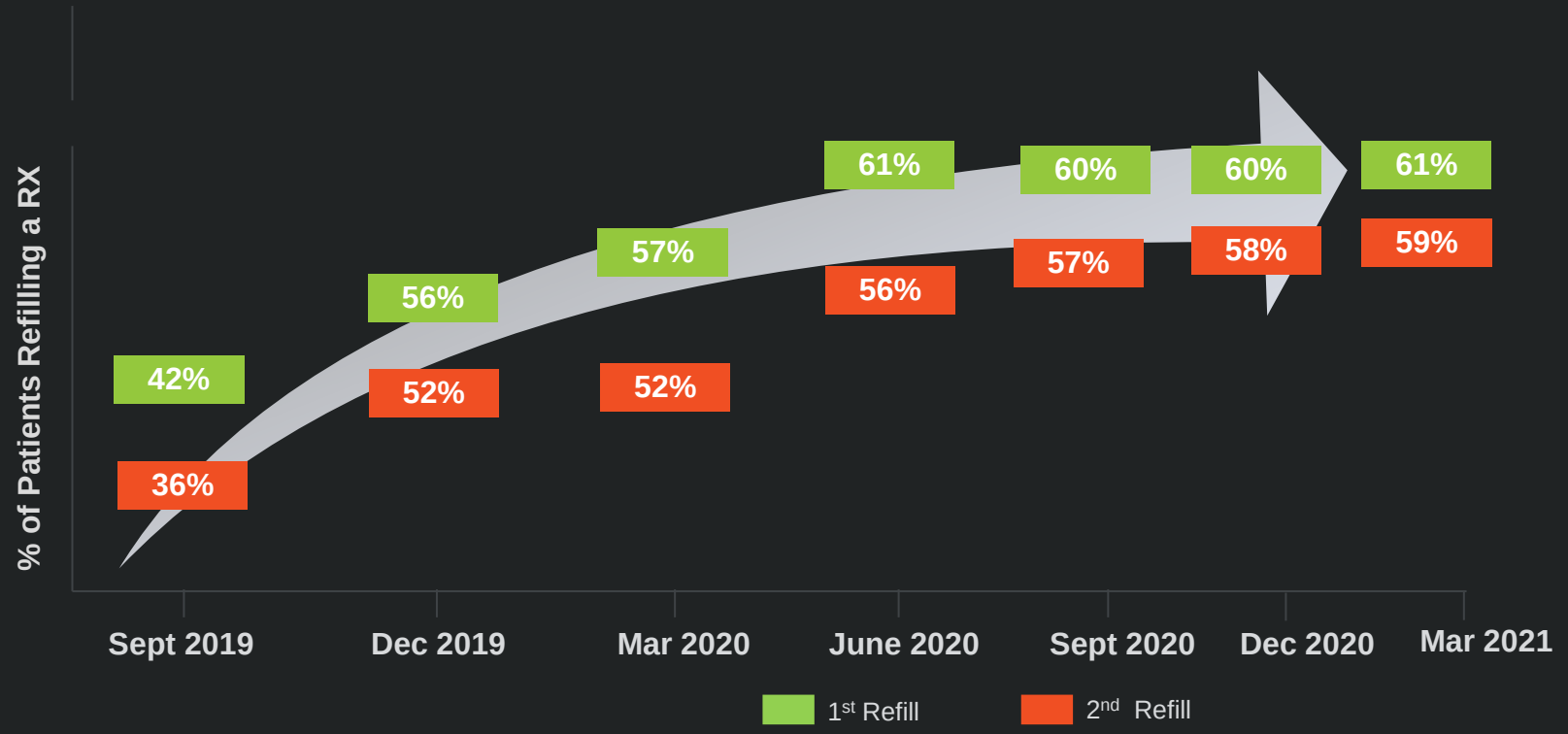
Monthly XPOVIO RXs Have Increased Sequentially Since Expanded XPOVIO FDA Approval



1,171 total RXs in Q1 2021 is highest quarterly demand since Q3 2019 launch

Key XPOVIO Patient Metrics[1]

Prescription Refill Rate for 1st and 2nd Prescription (Only Includes Patients Eligible for a Refill)



2.9

Average Treatment Cycles (RXs) Per Patient

12%

Patient Discontinuation Rate Due to Side Effects

[1] Based on patient data from Karyopharm's network of specialty pharmacy providers; prescription refill rates from Sept 2019-March 2021, average treatment cycles per patient and discontinuation rate due to side effects as of the end of March 2021

Karyopharm's Novel Pipeline | Selinexor

HEMATOLOGIC MALIGNANCIES | STUDY NAME	PHASE 1	PHASE 2	PHASE 3
Multiple Myeloma (relapsed/refractory) | **STORM**	**APPROVED[1]**		
Multiple Myeloma (relapsed/refractory) | **BOSTON[2]**	**APPROVED[1]**		
Diffuse Large B-cell Lymphoma (relapsed/refractory) | **SADAL**	**APPROVED[1]**		
Multiple Myeloma (relapsed/refractory and front-line) | **STOMP[3]**			
Diffuse Large B-cell Lymphoma (combination with rituximab-gemcitabine-dexamethasone-platinum (R-GDP)) **XPORT-DLBCL-030 (Phase 2/3)**			
Diffuse Large B-cell Lymphoma (combination with chemo and non-chemo regimens) | **XPORT-DLBCL-025[4]**			
Myelofibrosis (previously treated) | **XPORT-MF-035[4]**			
Myelofibrosis (combination with ruxolitinib)| **XPORT-MF-034[4]**			

Additional new Phase 3 study (XPORT-MM-031) evaluating XPOVIO in combination with pomalidomide and dexamethasone in patients with previously treated multiple myeloma expected to start in **2021**

[1] Full Prescribing Information and Medication Guide are available at www.XPOVIO.com [2] Oral selinexor, Velcade® (bortezomib) and dexamethasone vs. Velcade and dexamethasone. [3] Oral selinexor and dexamethasone + Revlimid® (lenalidomide), Pomalyst® (pomalidomide), Velcade®, Kyprolis® (carfilzomib) or Darzalex® (daratumumab). [4] Study expected to start in 2021.

Karyopharm’s Novel Pipeline | Selinexor

SOLID TUMOR MALIGNANCIES | STUDY NAME	PHASE 1	PHASE 2	PHASE 3
Liposarcoma (advanced unresectable dedifferentiated liposarcoma) | **SEAL**			
Endometrial Cancer (maintenance therapy) | **SIENDO**			
Melanoma (newly diagnosed or recurrent advanced – in combination with pembrolizumab) | **XPORT-MEL-033**			
NSCLC (combination with docetaxel) | **XPORT-STP-027**			
CRC (combination with pembrolizumab) | **XPORT-STP-027**			

GLIOBLASTOMA MULTIFORME (GBM) | STUDY NAME	PHASE 1	PHASE 2	PHASE 3
Glioblastoma (recurrent gliomas) | **KING**			
Glioblastoma (combination with active agents / newly diagnosed or recurrent) | **XPORT-GBM-029**			

Potential Endometrial Cancer Opportunity for XPOVIO

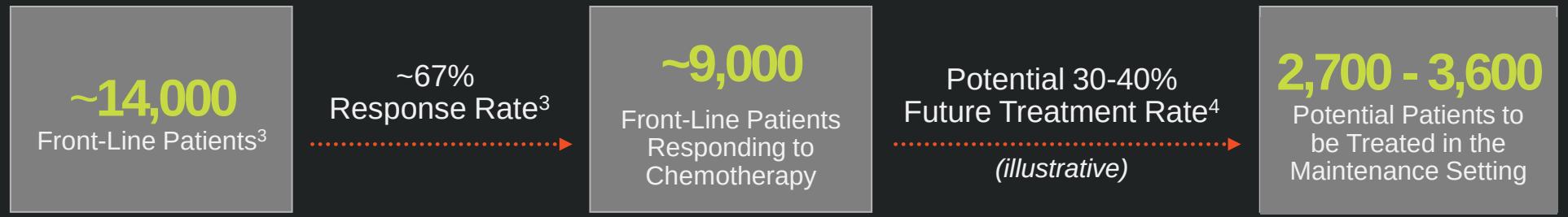
Overview and Epidemiology (US)

- Most common gynecologic cancer in the U.S with **>65K** cases and **>12K** deaths in 2020[1]
- While most woman are diagnosed with early-stage disease and have a good prognosis after surgery alone, **~14K** patients each year in the U.S. have advanced or metastatic disease and are treated with chemotherapy[2]

Current Treatment Paradigm

- Patients with Stage I-III disease are typically treated with surgery with or without radiation therapy (high-risk patients may also receive adjuvant chemotherapy)
- Patients with advanced or metastatic disease are typically treated with chemotherapy, most commonly a taxane plus platinum
  - Response rates (CR or PR) in the front-line setting can be as high as **67%**[3]
  - Patients then typically "watch and wait" until disease relapses
- In the second and later line settings, additional chemotherapy, immunotherapy and/or targeted agents are used
- There is currently **no drug therapy approved** in the maintenance setting, post front-line chemotherapy

Opportunity for Maintenance Therapy Post Front-Line Chemotherapy



[1] SEER / NCI Cancer Stat Facts. 2020. [2] EpicOncology™ Epidemeology Database, 2020. [3] Sorbe, B et al. Int J Gynecol Cancer. 2008 [4] 30-40% treatment rate is used for illustrative purposes and informed by actual maintence therapy rates seen in the ovarian cancer marketplace (note: % of ovarian cancer patients receiving mainenance therapy in the U.S.in 2020 was 43% as per Decision Resources Ovarian Cancer Disease Landscape Foreast Report, 2021)

Selinexor Was Previously Evaluated in a Phase 2 Study in Patients with Recurrent Gynecological Malignancies (SIGN Study)[1]

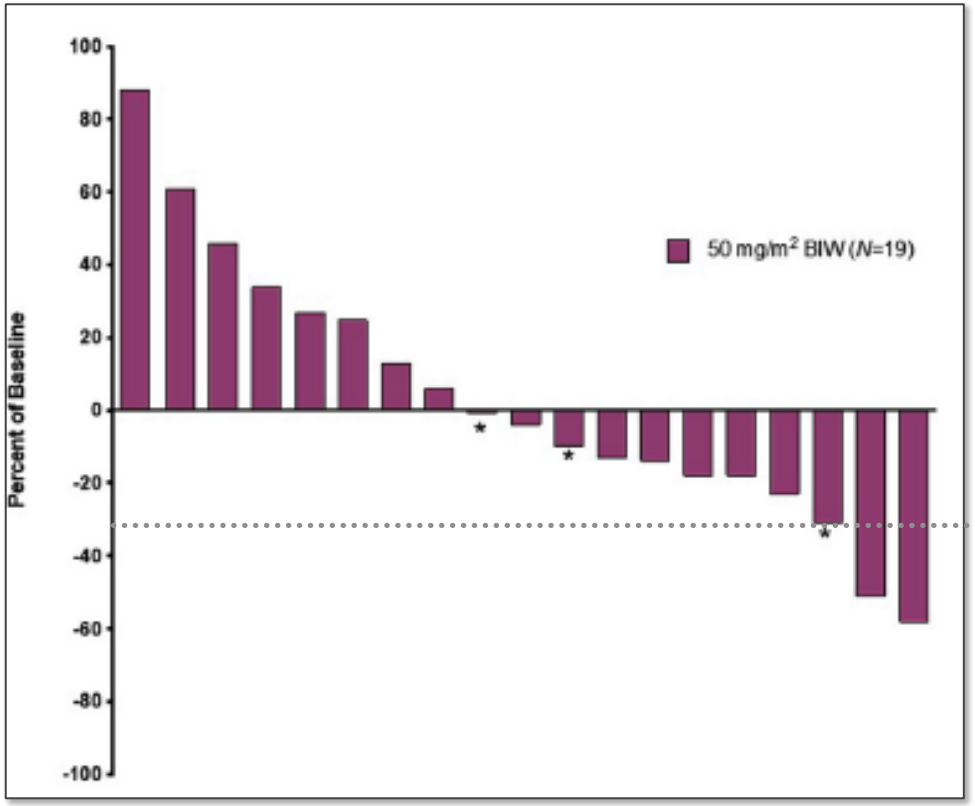
Baseline Patient Characteristics	
# of endometrial cancer patients in study	23
Previous lines of therapy (median, range)	2 (1-5)
Previous platinum agent Previous taxane	96% 100%
Endpoints	
Disease Control Rate (patients with PR or SD) Response Rate (confirmed PRs)	35% 9%

Note: 114 total patients enrolled in SIGN study with endometrial, ovarian and cervical cancers

Adverse Events (AEs)

Most common AEs across all patients were nausea, fatigue, decreased appetite, vomiting, weight loss, anemia, thrombocytopenia, dysgeusia, and blurred vision and were primarily grades 1 and 2. The most common grade 3 AEs were thrombocytopenia, fatigue, anemia, nausea and hyponatremia.

Endometrial Cancer Patients in SIGN Study



Waterfall plot of best percent change in the sum of all target lesions from screening for 19 evaluable patients with endometrial cancer.
* indicates platinum-refractory.

[1] Vergote I, et al. Gynecologic Oncology. 2019

SIENDO Study Design:

Phase 3 study evaluating once weekly selinexor as a maintenance therapy versus placebo in patients with endometrial cancer after first- or second-line chemotherapy

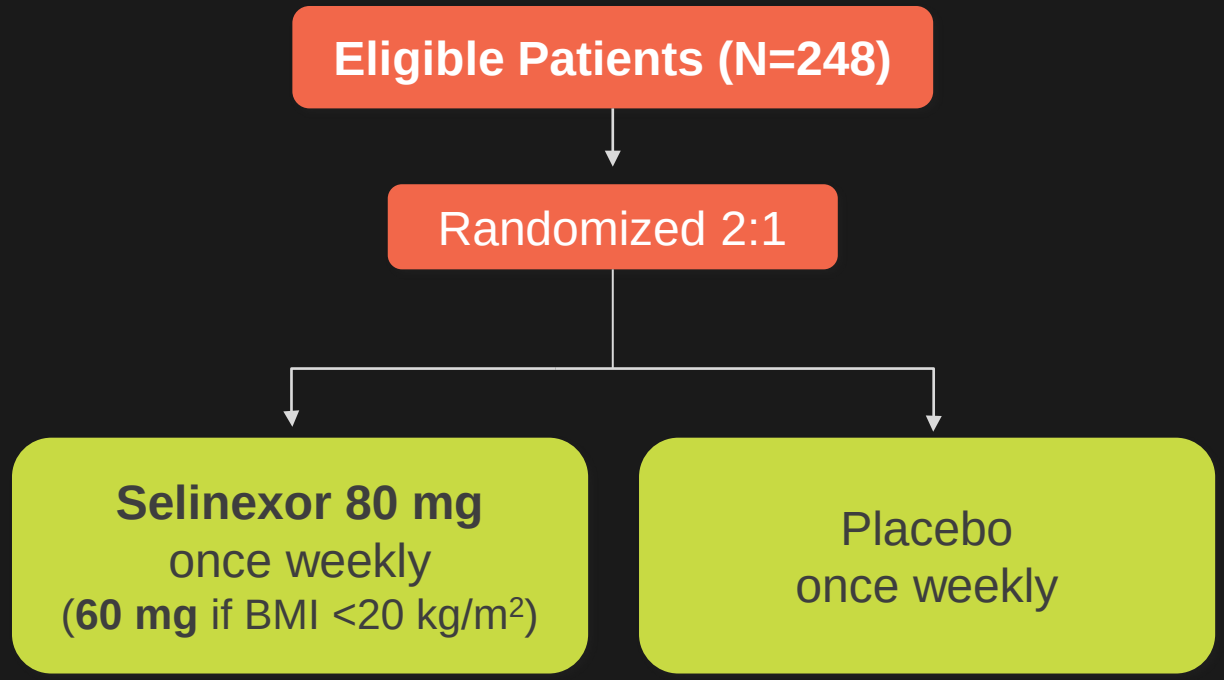
Eligibility

Patients who completed a single line of at least 12 weeks of taxane-platinum combination therapy including patients who received taxane-platinum combination therapy for:

- Primary Stage IV disease
- First Relapse (i.e., relapse after primary therapy including surgery and/or adjuvant therapy for Stage I-IV disease)

Primary Endpoint

- Progression-free survival from time of randomization until death or disease progression as determined by Investigator



- ***Trial passed interim futility analysis in November 2020***
- ***Top-line data expected by end of 2021***

First Quarter 2021 Financial Results

Mike Mason
Chief Financial Officer

First Quarter 2021 Financial Results

Statements of Operations	Three Months Ended March 31st	
	2021	2020
Total Revenue	$23.3M	$18.1M
XPOVIO Net Sales	$21.7M	$16.1M
License and other Revenue	$1.5M	$2.1M
Total Operating Expenses	$75.6M	$65.5M
Cost of Sales	$0.9M	$0.8M
Research and Development Expenses	$37.0M	$34.0M
Selling, General & Administrative Expenses	$37.7M	$30.7M
Net Loss	$57.4M ($0.77 per share)	$52.9M ($0.78 per share)

Balance Sheet and Financial Guidance

Balance sheet	March 31, 2021	December 31, 2020
Cash, Cash Equivalents, Restricted Cash and Investments	$233.6M	$276.7M

- Non-GAAP R&D and SG&A expenses are expected to be in the range of $280-300M for the full year 2021[1]
- Cash runway expected to be sufficient to fund planned operations into late 2022

[1] Excludes stock-based compensation expense. This outlook can only be provided on a non-GAAP basis 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.

Numerous Key Milestones Anticipated for 2021

1H 2021

1. CHMP opinion on STORM MAA ✓
2. Start of confirmatory Phase 3 Study in DLBCL in support of 2020 accelerated approval ✓
3. EMA conditional marketing authorization based on STORM data ✓
4. EMA submission of BOSTON study data (Type II variation) ✓
5. Increased U.S. XPOVIO sales following expanded FDA approval in multiple myeloma

2H 2021

1. SIENDO Phase 3 study fully enrolled and topline data announced
2. EMA expanded approval based on BOSTON study[1]
3. Initiation of Phase 3 study evaluating XPOVIO + pomalidomide in patients with multiple myeloma
4. Initiation of Phase 2 study evaluating XPOVIO + pembrolizumab in patients with metastatic melanoma
5. Additional combination data with XPOVIO and other standard of care anti-cancer drugs to be presented at medical meetings
6. Continued, increased U.S. XPOVIO sales

[1] Subject to regulatory approval(s)

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QUESTIONS?

Appendix

XPOVIO Net Product Sales Increased by 8% and Total Prescriptions (RXs) Increased by 17% in Q1 2021 Compared to Q4 2020