



Business Highlights & Second Quarter 2021 Financial Results

August 5, 2021

On Today's Call

- **Welcome**

Joseph Rayne, *Argot Partners*

- **Overview**

Richard Paulson, *President and Chief Executive Officer*

- **Commercial Highlights**

Sohanya Cheng, *SVP, Sales and Commercial Operations*

- **Clinical Pipeline Updates**

Jatin Shah, MD, *Chief Medical Officer*

- **Financial Summary and Guidance**

Michael Mason, *Chief Financial Officer*

- **Closing Remarks**

Richard Paulson, *President and Chief Executive Officer*

- **Q&A Session**

Joining for Q&A:

- **Stephen Mitchener, PharmD**

Chief Business Officer

- **Sharon Shacham, PhD**

Chief Scientific Officer

Forward-looking Statements and Other Important Information

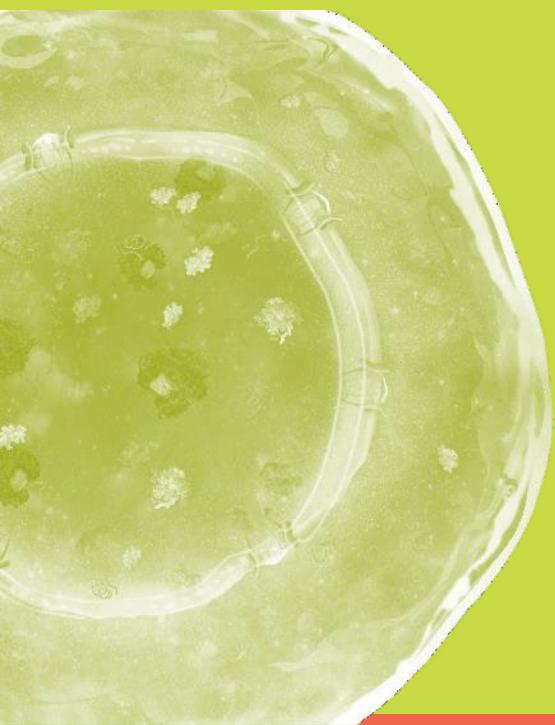
This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Karyopharm's guidance on its 2021 non-GAAP research and development and selling, general and administrative expenses; Karyopharm's expected cash runway; 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 and other hematologic malignancies and solid tumors; 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 Quarterly Report on Form 10-Q for the quarter ended March 31, 2021, which was filed with the Securities and Exchange Commission (SEC) on May 4, 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.

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Richard Paulson
Chief Executive Officer

OVERVIEW





Leveraging the inhibition of nuclear export as a mechanism to treat a broad range of cancers

XPOVIO[®]
(selinexor) 20 mg tablet

APPROVED IN THE US FOR 3 INDICATIONS¹

- Multiple myeloma as early as first relapse²
- Relapsed/refractory diffuse large B-cell lymphoma^{3,4}

Building on myeloma foundation

Driving depth and breadth of leadership presence in myeloma

Expanding global footprint

Expect CHMP review of MAA in 2L+ to be completed in 1H22

Key phase 3 solid tumor data remains on track

SIENDO top-line results in endometrial cancer expected by year end 2021

Powerhouse clinical pipeline

Targeting several high unmet need hematological and solid tumor cancers

Well-capitalized

Cash runway into mid-2023



Sohanya Cheng
*Head of Sales &
Commercial Operations*

COMMERCIAL HIGHLIGHTS

XPOVIO Launch Update: 2Q 2021

Continued Progress in 2L+ Market Uptake

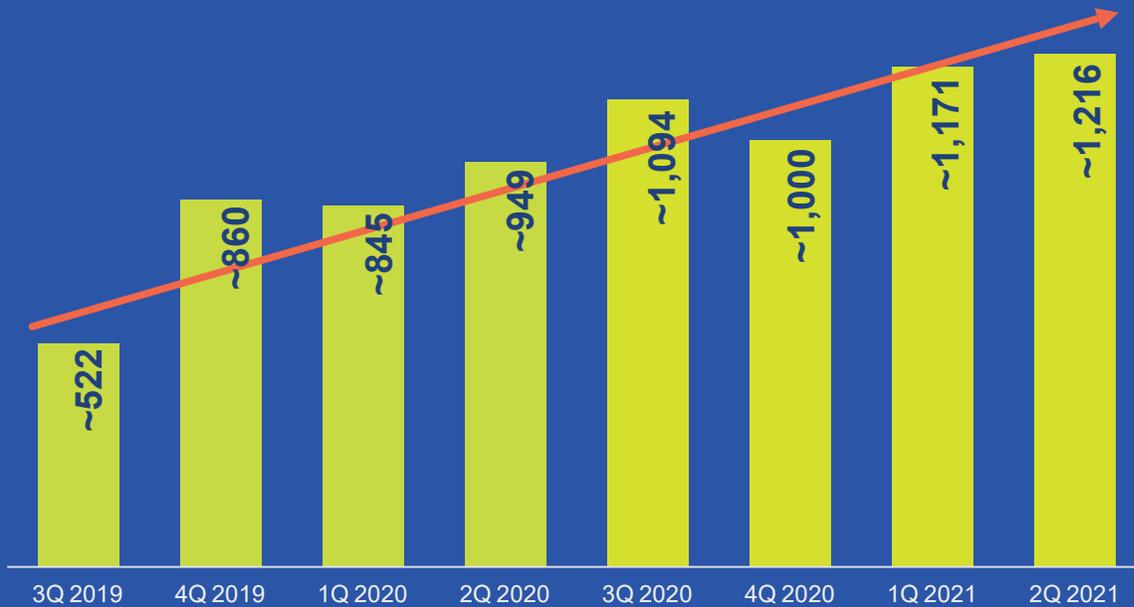
\$20.2M

XPOVIO US 2Q 2021
Net Product Revenues

~7,600

RXs filled as of June 30, 2021

XPOVIO RXs



2Q Highlights

- Sales up 8% vs 2Q20; 1H21 up 21% vs 1H20
- Unit demand up 28% in 2Q21 vs 2Q20; up 33% in 1H21 vs 1H20
- Rising confidence in physicians' overall perception¹; RXs actively evolving from penta-refractory to earlier lines²
- Prescribing accounts continue to increase; up 11% vs 1Q21
- Patients averaging 2.9 treatment cycles; still early days in 2L+
- ~97% of U.S. lives with confirmed access to XPOVIO, if prescribed
- Launched three new strength tablets (40mg, 50mg and 60mg)

Strategically Enhancing Commercial Capabilities

- Delaying and strengthening commercial team
- Added launch excellence capability and expertise
- Transforming data capabilities and partnership with external customers to identify the right patient at the right time
- Fine tuning messaging and positioning
- Focusing on strong execution in 2L+ myeloma and enhancing confidence and experience amongst prescribers
- Anticipate continuing to build momentum steadily into earlier lines and sustaining this momentum longer term as we advance our myeloma portfolio

US multiple myeloma landscape continues to improve outcomes for patients; is unique and complex:

- Strong innovation
- Patients are treated earlier; living longer
- Leading to an overall growing market
- Significant opportunity



Jatin Shah, MD
Chief Medical Officer

CLINICAL PIPELINE UPDATES

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

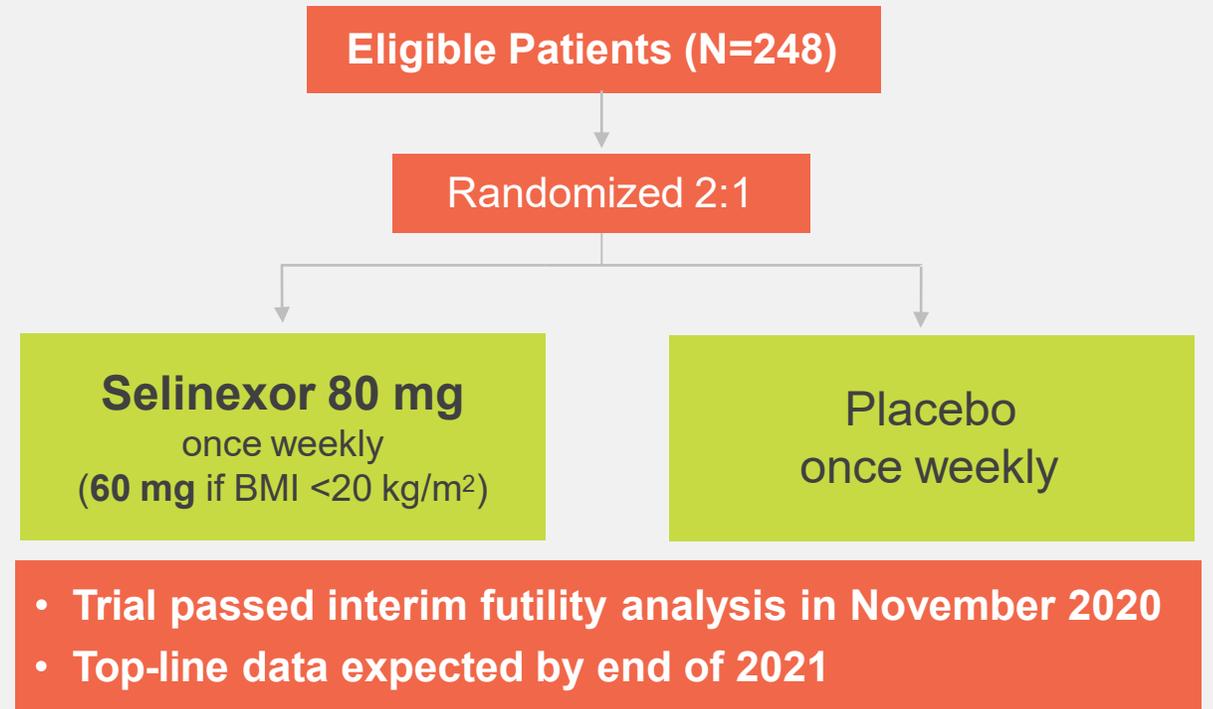
Eligibility

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



Opportunity For Maintenance Therapy Post Front-line Chemotherapy

~14,000

Front-Line Patients²
Not including <50% recurrent disease

~67%
Response
Rate³

~9,000

Front-Line Patients
Responding to Chemo

Estimated
40%–50%
Treatment
Rate⁴

~4,000

Est .Patients to be Treated
in the Maintenance Setting

Will increase over time with effective therapies

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 2020¹
- In the U.S., those diagnosed with early-stage disease generally have a good prognosis after surgery alone, however **~14K** patients each year in the front line will have advanced or metastatic disease and are treated with chemotherapy²

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)
- **20–30% Patients with advanced or metastatic disease typically treated with chemotherapy, 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 increasingly used
- There is currently **no drug therapy approved** in the maintenance setting, post chemotherapy in any setting

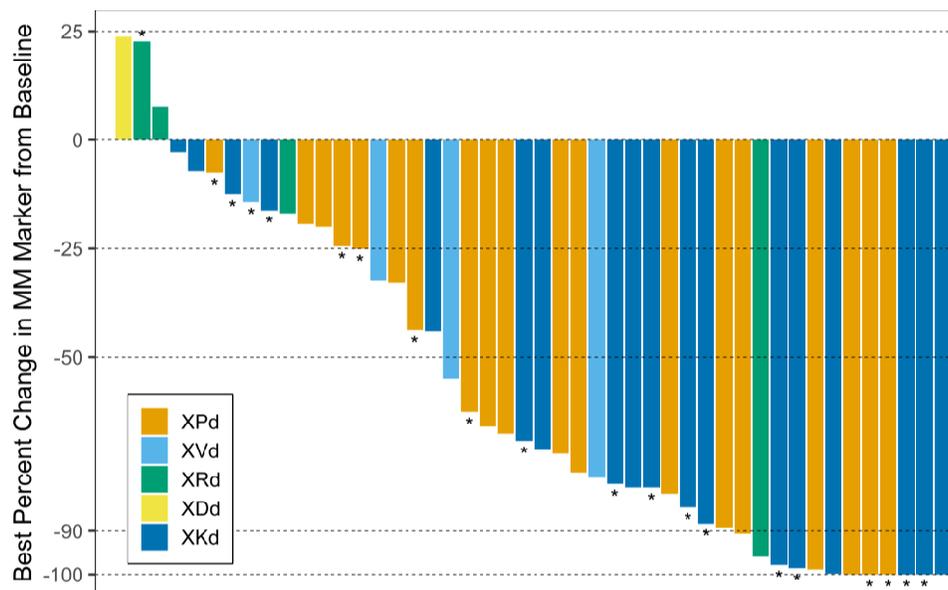
The background of the slide is a microscopic image of cells, likely cancer cells, showing their internal structures. The image is overlaid with a color gradient that transitions from blue on the left to orange on the right. A semi-transparent orange rectangular box is positioned on the right side of the slide, containing the main title text in white.

**Key 2Q 2021 Data
Presentations from
ASCO 2021 and EHA 2021**

Efficacy – XPOVIO Containing Regimens Post Anti-CD38 mAb Treatment

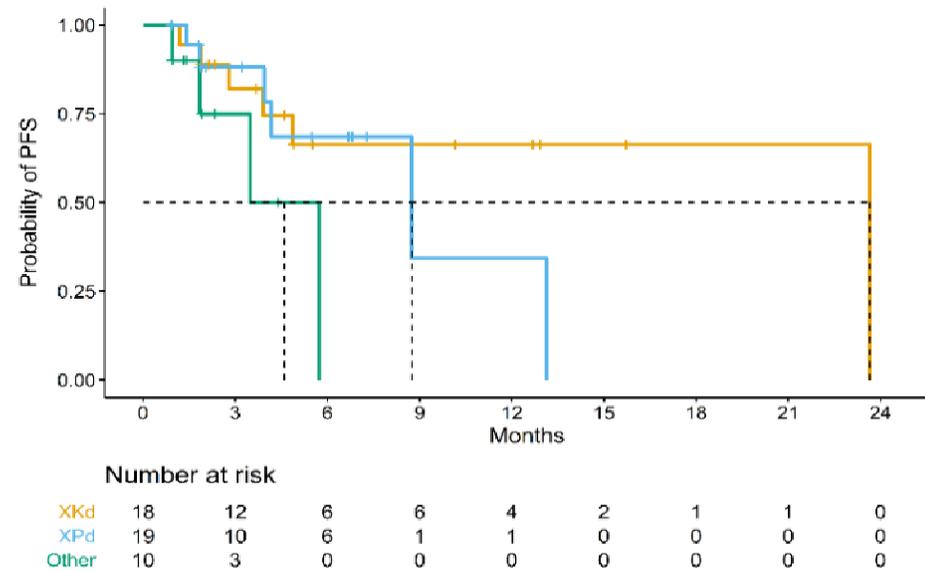
Waterfall Plot for Selinexor Triplets

Note: 1 XDd patient with +262% not shown; asterisk indicates del(17p), t(4;14), or t(14;16)



Progression-Free Survival by Selinexor Regimen

Patients previously treated with an anti-CD38 mAb



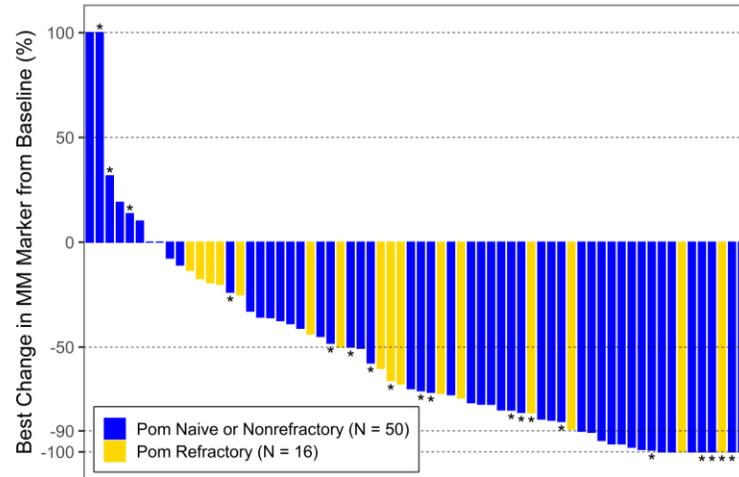
- Among all 47 evaluable patients ORR was 51.1% (24/47). ORR was 57.9% (11/19) in the XPd arm and 66.7% (12/18) in the XKd arm
- Similar ORRs were observed for patients who were naïve or non-refractory to the drug in the triplet administered in the current study whether they were treated with the α CD38 mAb in their most prior line or not
- The efficacy of selinexor-containing triplets was similar to that of the prior α CD38 mAb-containing regimen: ORR was 51.1% (24/47) in STOMP vs. 51.2% (21/41) for the prior regimen and median PFS was 13.1 months (95% CI, 4.9-not reached) in STOMP vs. 10.0 months (95% CI, 6.8-16.7 months) for the prior regimen
- The safety and efficacy of XPOVIO in combination with medications other than bortezomib and dexamethasone has not been established and other combination therapies are not approved by the US FDA or any other regulatory authority

XPd Efficacy Post Anti-CD38 mAb

Registrational Phase 3 Trial Starting by Year End 2021

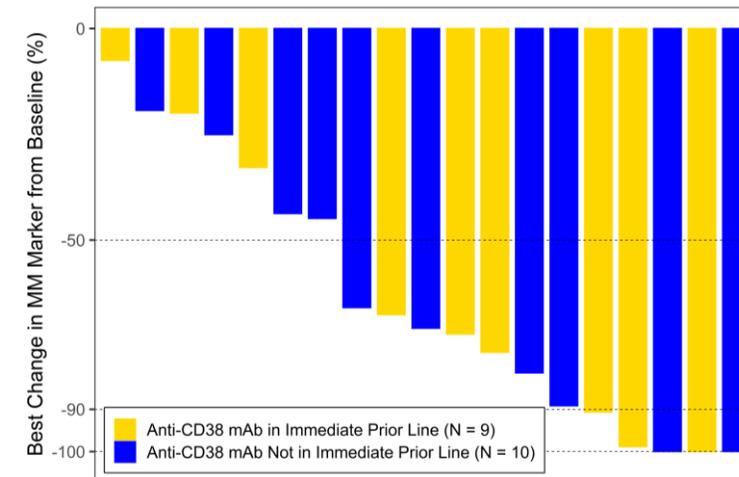
All Evaluable Patients

(N = 66, * = RP2D)



Patients Pretreated with Anti-CD38 mAb

(N = 19)



Best Responses in Evaluable XPd Patients		
	N	ORR
RP2D: Selinexor 60 mg QW + Pom 4 mg	20	13 (65.0)
Pom Refractory among all pts dosed	16	7 (43.8)
Pretreated with Anti- CD38 mAb	19	11 (57.9)

Responses were determined according to the International Myeloma Working Group (IMWG) criteria. Responses as of March 31, 2021, based on interim unaudited data

The safety and efficacy of XPOVIO in combination with medications other than bortezomib and dexamethasone has not been established and other combination therapies are not approved by the US FDA or any other regulatory authority

Phase 1b/2 STOMP Study – XPOVIO Plus Pomalyst® (pomalidomide) and Dexamethasone in Relapsed/Refractory Multiple Myeloma¹

Registrational Phase 3 Trial Starting by Year End 2021

- This all oral XPd combination appears highly active with durable responses
- No new safety signals identified
- These data support the planned Phase 3 study evaluating XPd in RRMM with prior therapies of PIs, IMiDs and anti-CD38 mAb (XPORT-MM-031)

	N	ORR	mPFS (months)	DOR (months)
RP2D²	20	65%	Not Reached	Not Reached
Pomalyst-naïve			12.2	24.2
Prior anti-CD38 mAb	19	58%	8.7	7.9

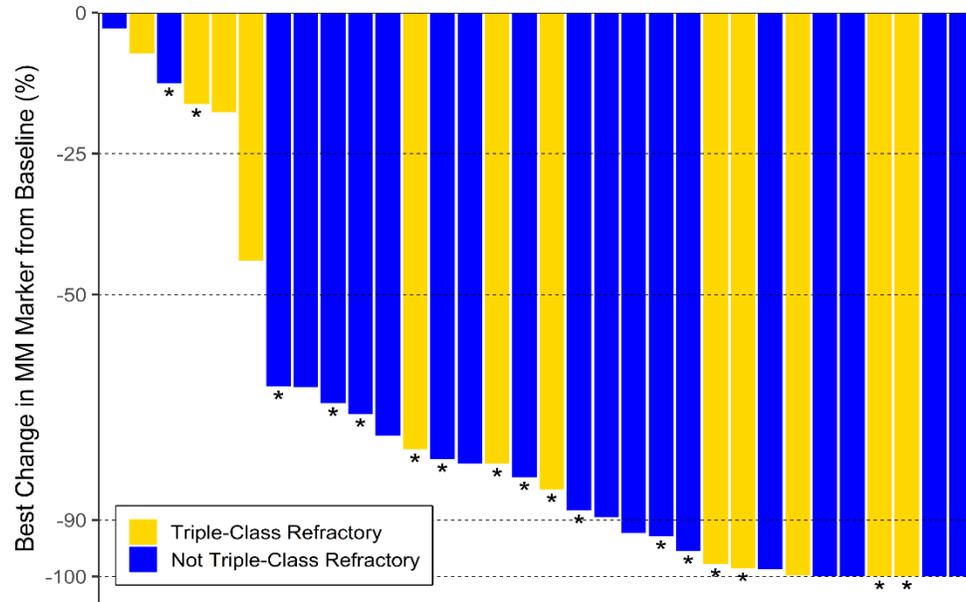
The safety and efficacy of XPOVIO in combination with medications other than bortezomib and dexamethasone has not been established and other combination therapies are not approved by the US FDA or any other regulatory authority

XKd Efficacy Post Anti-CD38 mAb

NCCN Guideline Pending

Waterfall Plot for All Dosed Patients

(* = High-Risk Cytogenetics)



Responses were determined according to the International Myeloma Working Group (IMWG) criteria. Responses as of April 22, 2021, based on interim unaudited data.

Best Response in Evaluable XKd Patients		
	N	ORR (%)
Overall	32	25 (78.1)
1–2 prior lines of therapy	8	7 (87.5)
≥3 prior lines of therapy	23	17 (73.9)
No high-risk cytogenetics	15	11 (73.3)
High-risk cytogenetics*	17	14 (82.4)

*Defined as any of del(17p), t(4;14), t(14;16), or gain 1q at initial diagnosis or screening.

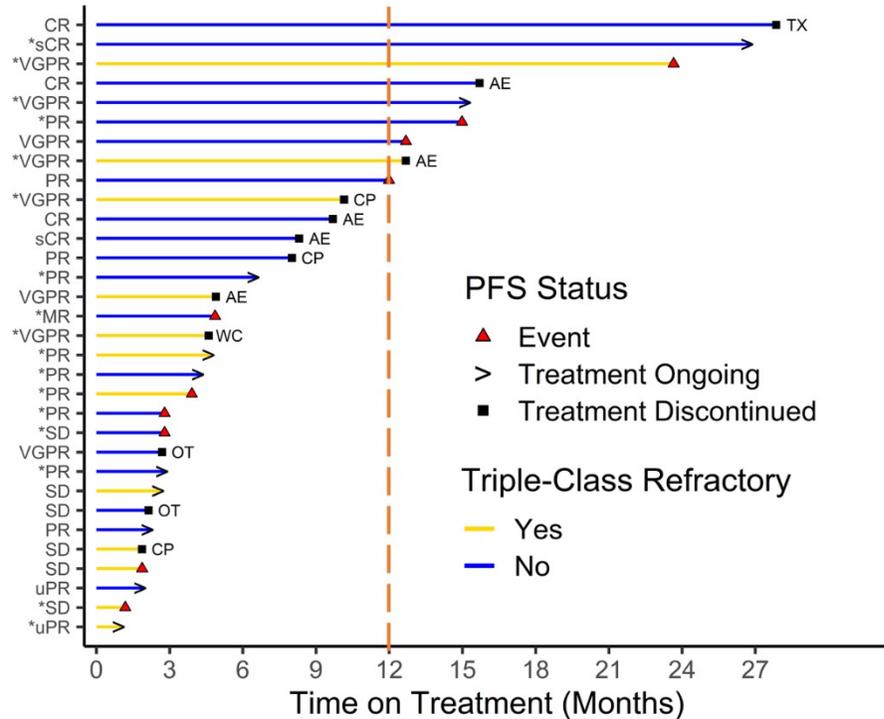
The safety and efficacy of XPOVIO in combination with medications other than bortezomib and dexamethasone has not been established and other combination therapies are not approved by the US FDA or any other regulatory authority

XKd Appears Highly Active: PFS in All Patients was 15.0 Months

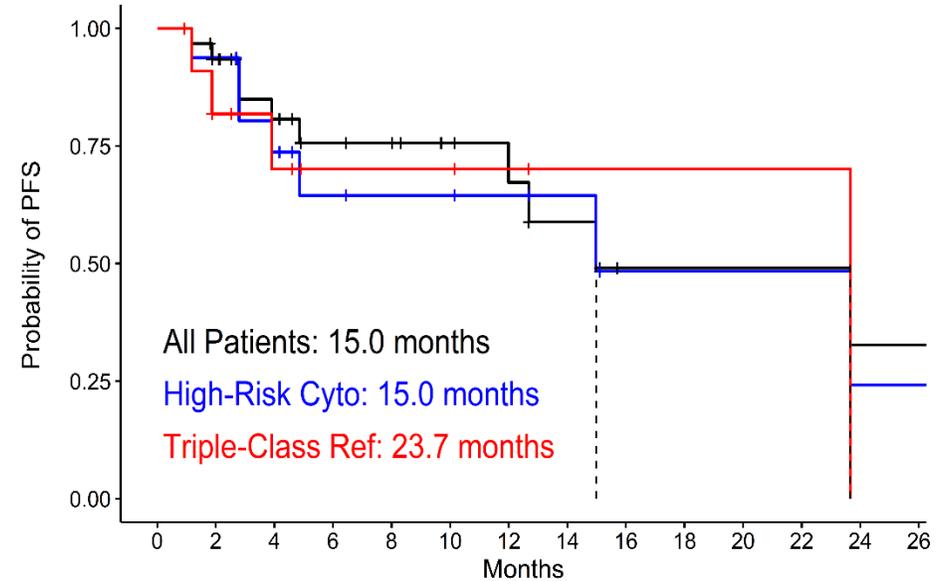
NCCN Guideline Pending

Swimmer Plot

(* = High-Risk Cytogenetics)



Progression-Free Survival



Number at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26
All Patients	32	27	19	14	13	10	8	6	3	3	3	3	2	2
High-Risk Cyto.	17	15	11	7	6	6	5	4	2	2	2	2	1	1
Triple-Class Ref.	12	8	6	3	3	3	2	1	1	1	1	1	0	0

TX = Toxicity to study drug; AE = Adverse event; CP = Disease Progression (Clinical Progression); WC = Withdrawal by patient; OT = Other

The safety and efficacy of XPOVIO in combination with medications other than bortezomib and dexamethasone has not been established and other combination therapies are not approved by the US FDA or any other regulatory authority

Phase 1b/2 STOMP Study – XPOVIO Plus Kyprolis® (carfilzomib) and Dexamethasone in Relapsed/Refractory Multiple Myeloma¹

- The XKd combination appears highly active and durable
- No new safety signals identified

	N	ORR	mPFS (months)
All evaluable patients	32	78%	15.0
≥3 prior lines of therapy	23	74%	23.7
High-risk cytogenetics	15	73%	15.0

The safety and efficacy of XPOVIO in combination with medications other than bortezomib and dexamethasone has not been established and other combination therapies are not approved by the US FDA or any other regulatory authority

Phase 3 BOSTON Study – Older/Frail Patients with Previously Treated Multiple Myeloma¹

- Once weekly XVd was associated with significant survival benefit, prolonged PFS, improved response rates and lower rates of peripheral neuropathy, compared to Vd

In older, frail patients ≥65 Years	XVd	Vd	P-value	Hazard Ratio
Overall survival	Not reached	28.6 months	p=0.012	0.60; 95% CI, 0.38-0.94
Progression-free survival	21.0 months	9.5 months	p=0.002	0.55; 95% CI, 0.37-0.83
Overall response rate	76.1%	64.4%	p=0.024	–
Peripheral neuropathy	32%	47%	p=0.001	–
Grade ≥2 peripheral neuropathy	21%	34%	p=0.001	–

Age group (<65 vs. ≥65) was a pre-specified subgroup factor in statistical analysis plan (SAP)

Results

Clinical

5-HT3 Antagonist

All patients should receive ondansetron 8 mg or equivalent, unless contraindicated, orally 1 hour before each dose of selinexor and q 8 hours for 2 days post selinexor for the first 2 cycles of the study

AND

Olanzapine

Olanzapine 5 mg PO or equivalent every day, for **the first 2 months** of the study or longer if needed.

Or

NK-1R Antagonist

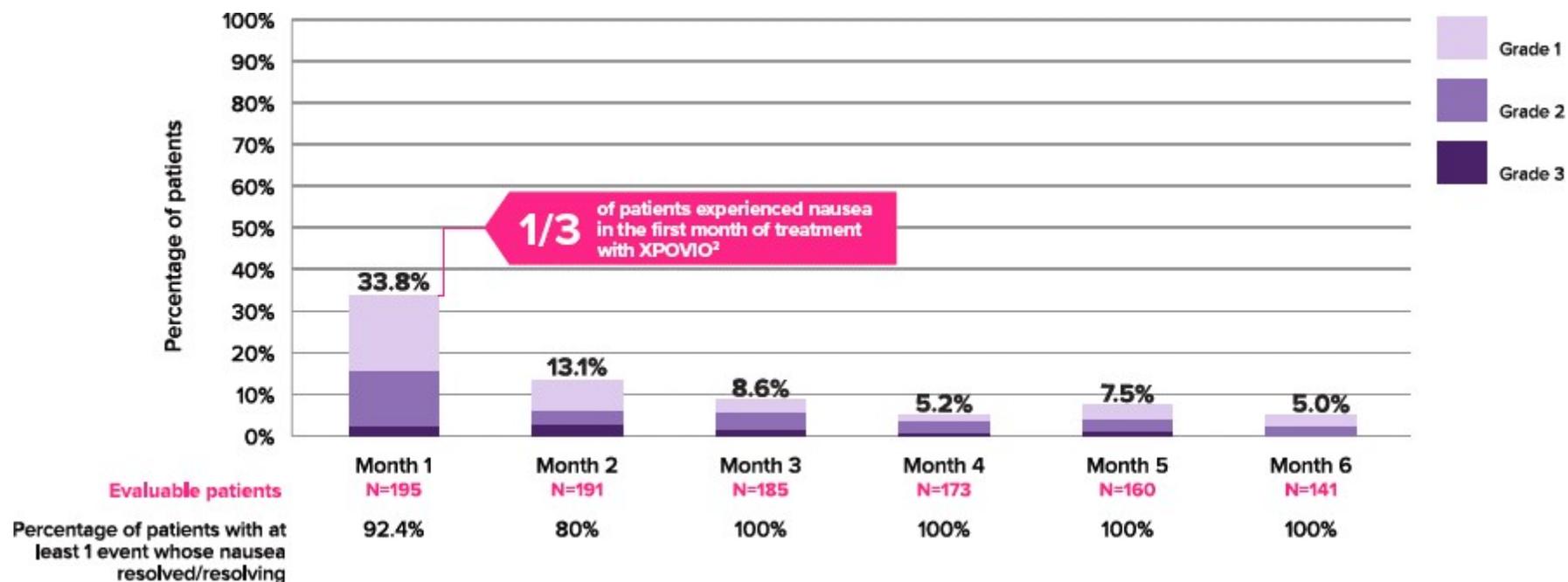
An NK1 receptor antagonist can be used together with ondansetron for the first 2 cycles or longer if needed.

- Patients may taper supportive care at treating physician's discretion after 2 cycles of therapy

Treatment-related Nausea with XVd* is Generally Manageable and Transient^{1,2}

- Percentage of patients experiencing nausea decreased in the first month of XVd using appropriate antiemetic measures
- XPOVIO dosing in the BOSTON trial was 100mg taken orally, once weekly
- The BOSTON trial only required one anti-emetic, a 5HT3

Percentage of patients experiencing nausea events per month in the XVd arm of BOSTON trial



*XVd=XPOVIO + bortezomib and dexamethasone (Vd).

Phase 1 Study Eltanexor in Myelodysplastic Syndrome¹

- Single-agent eltanexor appears active in patients with high-risk MDS that is primary refractory to hypomethylating agents
- Median OS of 9.9 months

	Eltanexor (10mg) N=5	Eltanexor (20mg) N=10	Total N=15
ORR (mCR +HI)	60%	50%	53%
Treatment duration (weeks)	15.0	12.5	13.0
Median time to response (weeks)	8.1	9.1	8.4
Median duration of response (95% CI) (months)	1.81 (NA, NA)	5.82 (3.02, NA)	4.42

The safety and efficacy of eltanexor in myelodysplastic syndrome not been established and has not been approved by the US FDA or any other regulatory authority

Advancing Pipeline Across Multiple High Unmet Needs



¹ Versus elotuzumab and pomalidomide. ² Study expected to start in 2021. ³ Sponsored by European Myeloma Network. ⁴ Oral selinexor and dexamethasone + Revlimid® (lenalidomide), Pomalyst® (pomalidomide), Velcade®, Kyprolis® (carfilzomib) or Darzalex® (daratumumab). ⁵ XPORT-DLBCL-030 is a Phase 2/3. ⁶ XPORT-MF-034 is a Phase 1/2. ⁷ XPORT-CRC-041 and XPORT-NSCLC-039 are supported by Phase 1 data from XPORT- S TP-027.



MICHAEL MASON
Chief Financial Officer

**FINANCIAL SUMMARY
AND GUIDANCE**

Second Quarter 2021 Financial Results

Statements of Operations (\$ millions)	2Q 2021	2Q 2020
Total Revenue	\$22.6	\$33.5
XPOVIO Net Sales	\$20.2	\$18.6
License and other Revenue	\$2.4	\$14.9
Total Operating Expenses	\$71.6	\$73.8
Cost of Sales	\$1.1	\$0.4
Research and Development Expenses	\$34.0	\$42.6
Selling, General & Administrative Expenses	\$36.5	\$30.8
Net Loss	\$53.6	\$46.4
Net Loss (per share)	(\$0.71)	(\$0.63)

Balance sheet (\$ millions)	June 30, 2021	December 31, 2020
Cash, Cash Equivalents, Restricted Cash and Investments	\$239.3	\$276.7

2021 Financial Guidance

	FY 2021
Non-GAAP Combined R&D and SG&A Expenses¹	\$270M – \$290M

- Received \$60 million in expanded royalty agreement with entities managed by HealthCare Royalty Management, LLC, with up to another \$40 million in potential financing available
- Cash runway expected to be sufficient to fund planned operations into mid-2023

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.

Richard Paulson
Chief Executive Officer

CLOSING REMARKS



ENHANCING CAPABILITIES, EVOLVING THE ORGANIZATION AND LOOKING AHEAD TO A CATALYST-DRIVEN 2H 2021

1H 2021 Achievements

1. Increased U.S. XPOVIO sales following expanded FDA approval in multiple myeloma
2. Commenced organizational changes to enhance commercial capabilities
3. Secured \$60M additional funding
4. Attained conditional marketing approval in Europe and UK for penta-refractory STORM population
5. EMA validation of BOSTON MAA (Type II variation)
6. Commenced confirmatory Phase 3 Study in DLBCL in support of 2020 accelerated approval
7. First patients dosed in two new company-sponsored trials evaluating selinexor either alone or in combination with approved agents in melanoma and myelofibrosis

2H 2021 Milestones

1. Continue to enhance commercial capabilities; continue to increase U.S. XPOVIO sales
2. Initiation of Phase 3 study evaluating XPOVIO + pomalidomide in patients with multiple myeloma
3. SIENDO Phase 3 top-line data announced
4. Initiation of key late-stage clinical studies in MDS, NSCLC, myelofibrosis, and CRC
5. Additional combination data in hematologic and solid tumor malignancies with XPOVIO and other standard of care anti-cancer drugs to be presented at ESMO 2021 and other medical meetings
6. Host investor day to outline strategic imperative and pipeline priorities

Q&A SESSION



The image features a microscopic view of numerous cells, likely stained for histology, showing intricate internal structures. The background is a gradient of blue and purple. An orange semi-transparent rectangular overlay is positioned on the right side of the image, containing the word "Appendix" in white text.

Appendix

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	96%
Previous taxane	100%

Endpoints

Disease Control Rate (patients with PR or SD)	35%
Response Rate (confirmed PRs)	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.

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Endometrial Cancer Patients in SIGN Study

