Karyopharm® Therapeutics

JP Morgan Healthcare Conference 2021

Michael G. Kauffman, MD, PhD,
Chief Executive Officer

January 11, 2021

Forward-looking Statements and Other Important Information

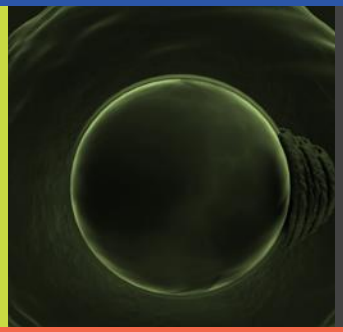
This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Karyopharm's expectations and plans relating to XPOVIO for the treatment of patients with relapsed or refractory multiple 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 agree that selinexor qualifies for conditional approval in the E.U. as a result of data from the STORM study or confirmatory approval in the E.U. based on the BOSTON study in 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 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 obtain and maintain requisite regulatory approvals and to enroll patients in its clinical trials; unplanned cash requirements and expenditures; development of drug candidates by Karyopharm's competitors for indications in which Karyopharm is currently developing its drug candidates; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any drug candidates it is developing. These and other risks are described under the caption "Risk Factors" in Karyopharm's Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, which was filed with the Securities and Exchange Commission (SEC) on November 2, 2020, and in other filings that Karyopharm may make with the SEC in the future. Any forward-looking statements contained in this presentation 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 accelerated approval 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.

XPOVIO®(selinexor) is a registered trademark of Karyopharm Therapeutics Inc. Any other trademarks referred to in this presentation are the property of their respective owners. All rights reserved.

Karyopharm at a Glance

Commercial-stage, global pharmaceutical company with **one FDA-approved drug** in **three oncology indications** and **three** additional drug candidates in clinical development

Industry leader in targeting **nuclear export dysregulation** as a mechanism to treat cancer



XPOVIO® (selinexor) received first accelerated approval from the FDA in July 2019 (penta-refractory multiple myeloma)

In December 2020, XPOVIO received expanded FDA approval in patients with multiple myeloma **as early as first relapse**

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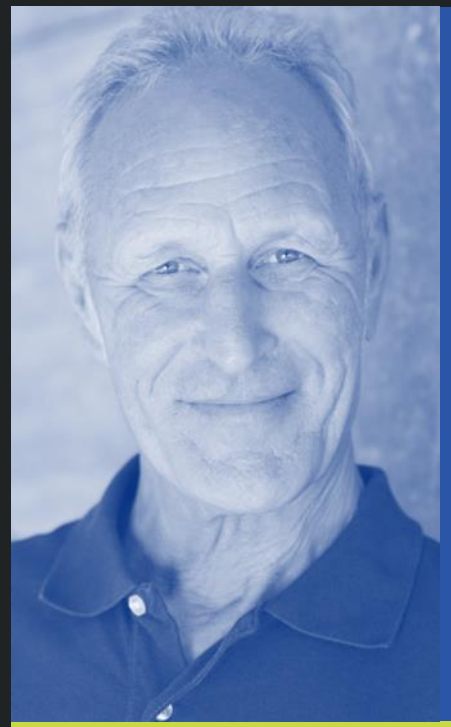
Karyopharm at a Glance

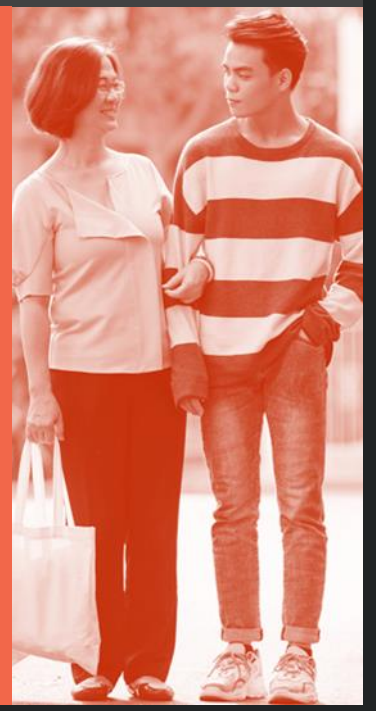


XPOVIO also received accelerated approval in June 2020 for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

All programs developed in-house

Numerous key milestones expected over the next 12 months

Ongoing clinical development for XPOVIO and next-generation programs in earlier lines of treatment, in combination trials, and in **additional tumor types** across both **hematologic and solid tumor malignancies**



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XPOVIO Now Approved In Significantly Expanded Multiple Myeloma (MM) Patient Population

FDA Expanded Approval on December 18, 2020

XPOVIO is the **FIRST** and **ONLY** nuclear export / XPO1 inhibitor approved by the FDA

Full Prescribing Information and Medication Guide available at www.XPOVIO.com

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[1] XPOVIO (selinexor) package insert

XPOVIO Received Accelerated Approval in Relapsed or Refractory DLBCL

XPOVIO is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy[1]

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Full Prescribing Information and Medication Guide are available at XPOVIO.com

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[1] XPOVIO (selinexor) package insert

Safety Highlights from the XPOVIO Prescribing Information[1]

No Black Box Warnings

No Contraindications

Patient Medication Guide

Warnings and Precautions

- Thrombocytopenia
- Neutropenia
- Gastrointestinal Toxicity
- Hyponatremia
- Serious Infection
- Neurological Toxicity
- Embryo-Fetal Toxicity
- Cataract

Monitoring Instructions and Recommended Concomitant Treatments

- Monitor complete blood count (CBC) with differential, standard blood chemistries, body weight, nutritional status, and volume status at baseline and during treatment as clinically indicated. Monitor more frequently during the first three months of treatment.
- Patients advised to maintain adequate fluid and caloric intake throughout treatment. Consider intravenous hydration for patients at risk of dehydration.
- Provide prophylactic antiemetics. Administer a 5-HT3 receptor antagonist and other anti-nausea agents prior to and during treatment with XPOVIO
- Recommended XPOVIO dosage reductions and dosage modifications for adverse reactions are included in the Prescribing Information

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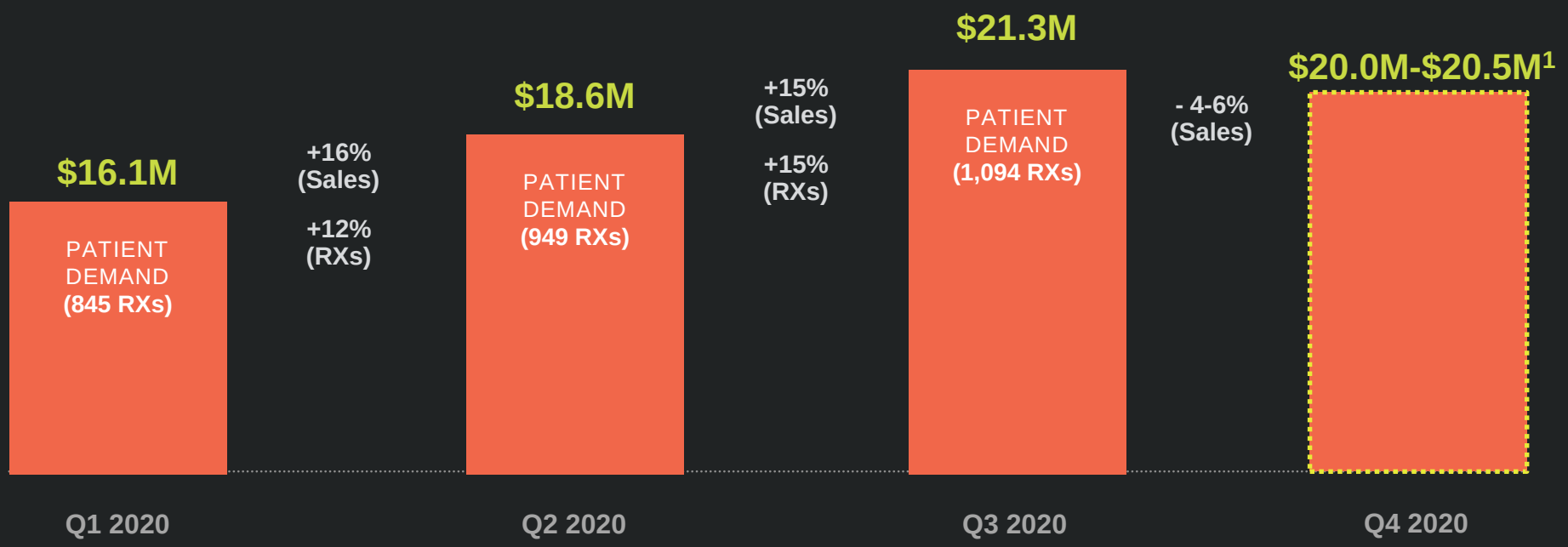
[1] XPOVIO (selinexor) package insert

XPOVIO 2020 Quarterly Sales and Prescription (RX) Trends

XPOVIO Product Sales and RXs in 2020



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[1] Preliminary unaudited fourth quarter 2020 sales

Update on Estimated Q4 and Full Year 2020 Revenues and XPOVIO Sales[1]

- Q4 2020 revenues estimated to be $35.0M - $36.0M; Full year 2020 revenues estimated to be $108.0M - $109.0M
  - $20.0M - $20.5M in Q4 2020 XPOVIO sales
  - ~$5M payment from FORUS Therapeutics, Inc. for commercial rights to XPOVIO in Canada
  - ~$10M payment from Antengene for regulatory milestones achieved in the Asia-Pacific region
- Q4 XPOVIO sales primarily affected by:
  1. Surge in U.S. COVID-19 cases
     - Fewer patient visits to their health care providers
     - Reduced ability of Karyopharm commercial team to access customers in-person
  2. Increased competition in the penta-refractory multiple myeloma and 3rd line+ DLBCL patient settings
- Strong return to sales growth seen in December following declines in October and November of 2020
  - Positive sales momentum seen in December 2020 following NCCN guideline update adding three XPOVIO regimens to its treatment recommendations and the expanded FDA approval granted on December 18th

Following XPOVIO's FDA expanded approval in multiple myeloma
(**5X** number of eligible patients and **3X** expected duration of treatment relative to initial indication),
Karyopharm expects to return to XPOVIO quarterly sales growth beginning in Q1 2021

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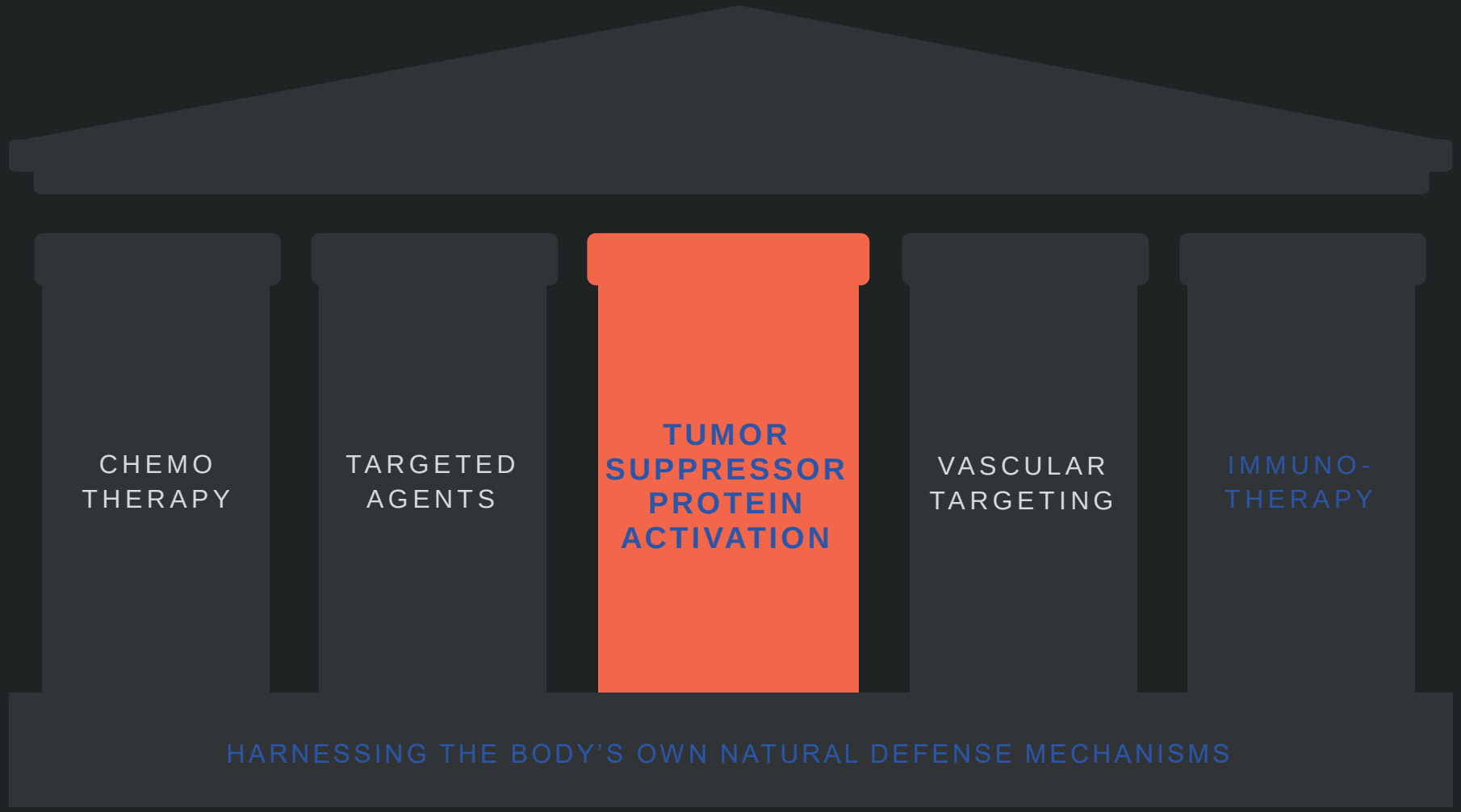
[1] Preliminary unaudited fourth quarter and full year 2020 sales

INNOVATIVE APPROACH TO TARGETING CANCER

Core Pillars of Cancer Drug Therapy



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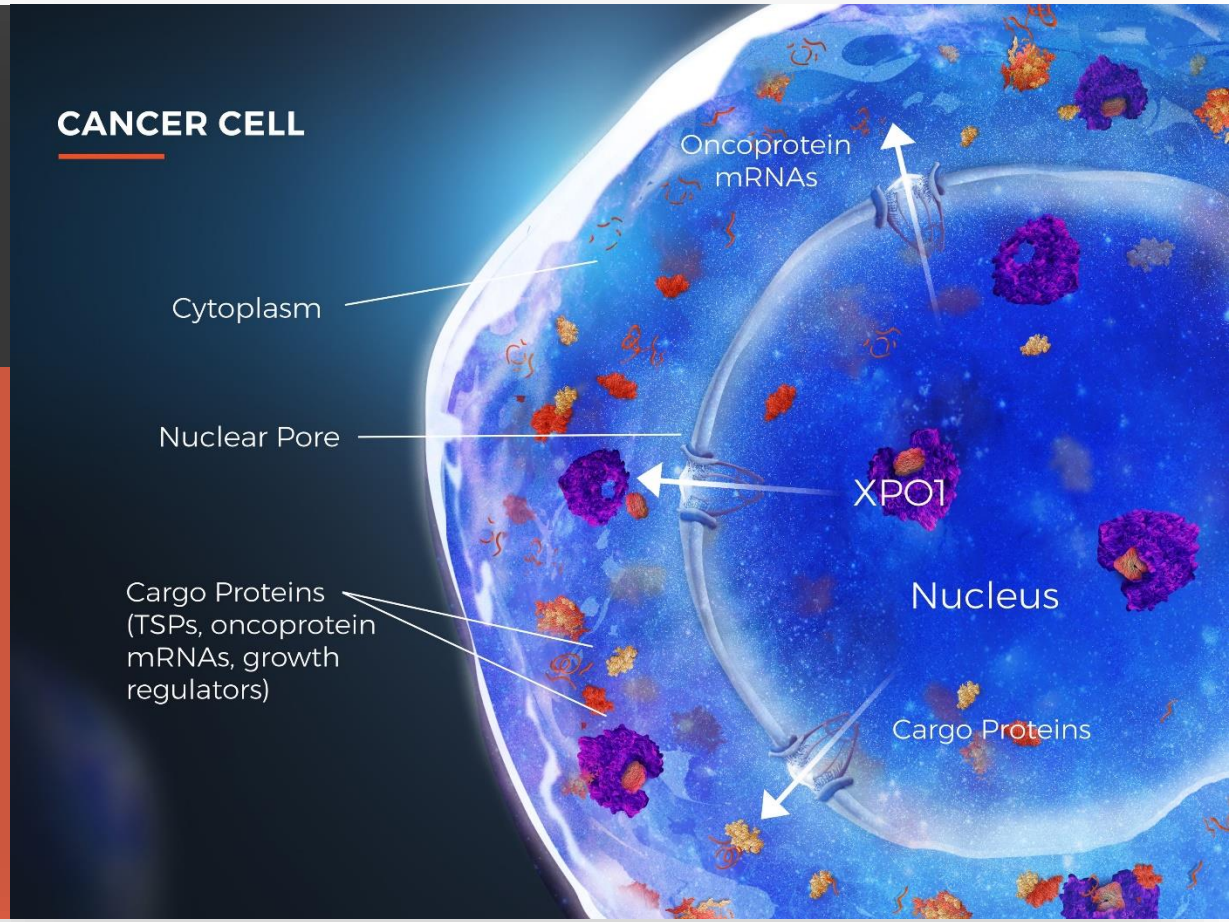
XPOVIO® (selinexor) / SINE Mechanism of Action: Inhibition of XPO1[1-4]

XPO1 OVEREXPRESSION

- Enables cancer cells to escape tumor suppressor proteins (TSPs) mediated cell cycle arrest and induction of apoptosis
- Correlates with poor prognosis and drug resistance

INHIBITION OF XPO1 IMPACTS TUMOR CELLS VIA 3 CORE MECHANISMS

1. Increases nuclear levels and activation of TSPs
2. Traps oncoprotein mRNA in the nucleus leading to reduced oncoprotein levels
3. Retains activated glucocorticoid receptor in the nucleus



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[1] Gupta A, et al. J Thorac Oncol. 2017. [2] Sun Q, et al. Signal Transduct Target Ther. 2016.
[3] Gandhi UH, et al. Clin Lymphoma Myeloma Leuk. 2018. [4] Gravina GL, et al. J Hematol Oncol. 2014

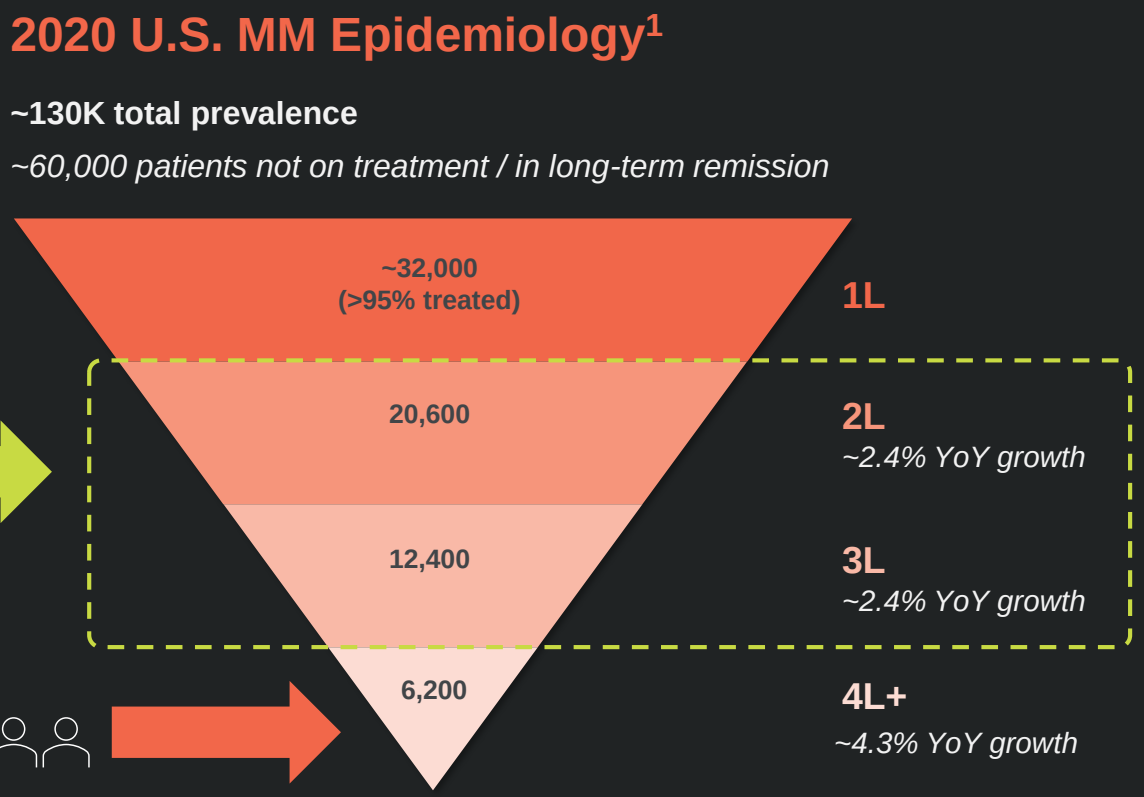
MULTIPLE MYELOMA

XPOVIO's December 2020 Approval (BOSTON Study) Expands Addressable Population by **5X**

BOSTON approval:
33,000 (in the 2nd and 3rd Line)

Expands addressable population by **5X**

STORM approval:
~6,000 (in the 4th Line+)



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[1] Sources: Decision Resources used for growth rates for treated patients and overall prevalence; Kantar Cancer Impact; SEER; Cancer Facts and Figures 2020

XPOVIO's December 2020 Approval (BOSTON Study) Extends Duration of Treatment by **3X**

	Median # of Prior Therapies	XPOVIO Dose Frequency	ORR	Median Progression Free Survival (in months)	Mean Duration of Treatment (in months)
STORM Study[1,2] (Penta-Refractory)	8	**Twice per week** (in combination with dexamethasone)	25%	3.7	3
BOSTON Study[3] (1–3 Prior Therapies)	2	**Once per week** (in combination with once-weekly Velcade and dexamethasone)	76%	13.9	10

BOSTON approval extends duration of treatment by **3X**

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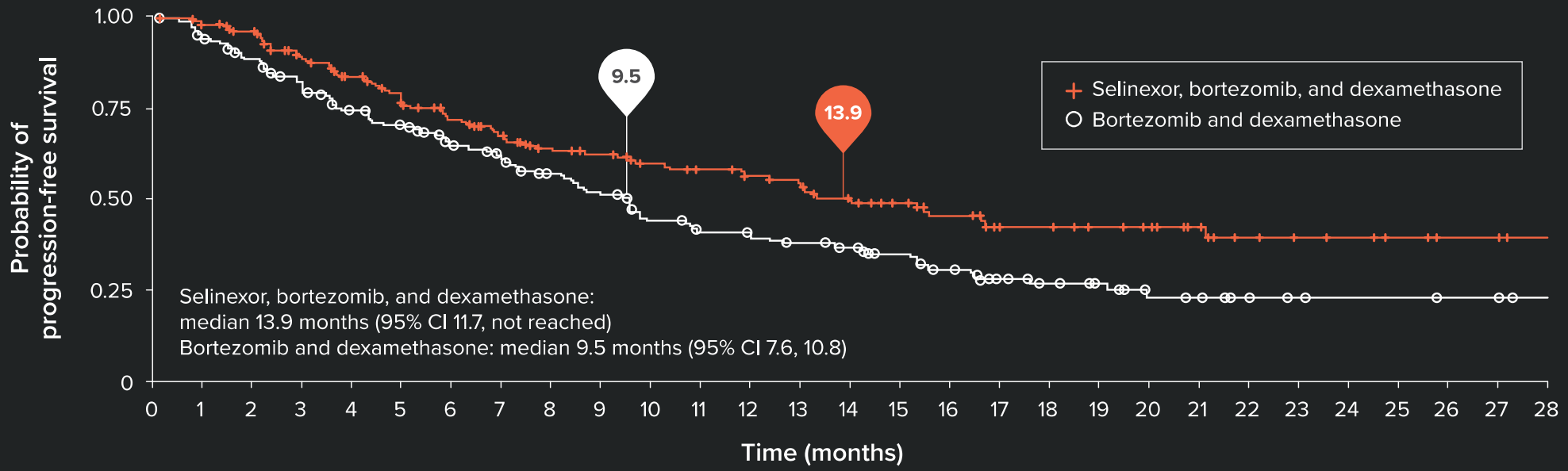
[1] STORM study provided the basis for XPOVIO's approved indication in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors (PI), at least 2 immunomodulatory agents (IMiD), and an anti-CD38 monoclonal antibody (mAb). [2] XPOVIO Prescribing Information and Chari et al., NEJM. August 2019. [3] Grosicki S, et al. Lancet. 2020.

Progression Free Survival (PFS) Significantly Longer with XVd Compared to Vd

30% reduction in risk of progression or death[1]

Hazard ratio: 0.70
(96% CI 0.5-0.93), *p*=0.0075

ONCE-WEEKLY, ORAL XPOVIO + VD DELIVERED AN EARLY AND SUSTAINED PFS ADVANTAGE VERSUS TWICE-WEEKLY Vd[1]



Hazard ratio (HR) is based on stratified Cox's proportional hazard regression modeling, p-value based on stratified log-rank test.

*According to the International Myeloma Working Group (IMG Uniform Response Criteria for Multiple Myeloma, as assessed by an Independent Review Committee (IRC). XVd=XPOVIO® (selinexor) with Velcade® (bortezomib) and dexamethasone; Vd=Velcade and dexamethasone.

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[1] XPOVIO (selinexor) package insert

Overall Response Rates (ORR) Demonstrated in the BOSTON Trial[1]:

Responses observed with oral, once-weekly XPOVIO + Vd were rapid and durable versus twice-weekly Vd[1]

MEDIAN TIME TO RESPONSE[1]

1.4 MONTHS once-weekly XPOVIO + Vd

VS

1.6 MONTHS twice-weekly Vd

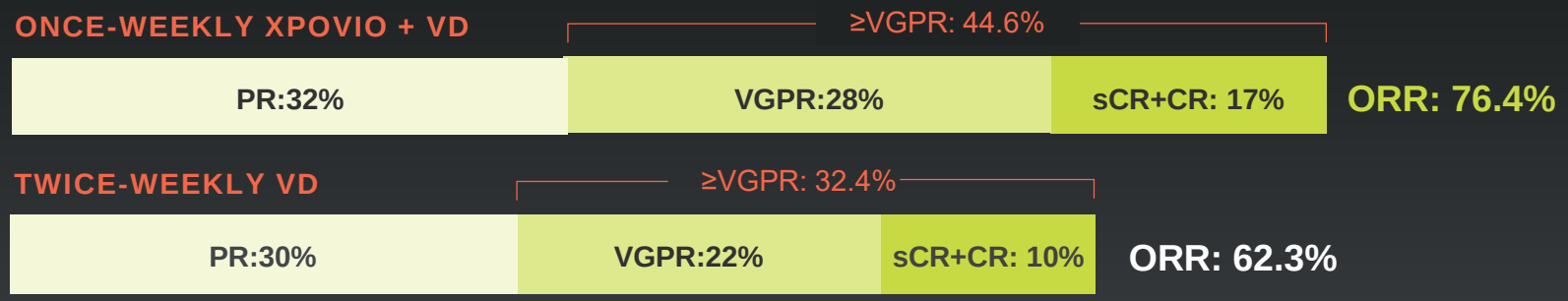
MEDIAN DURATION OF RESPONSE[1]

20.3 MONTHS once-weekly XPOVIO + Vd

VS

12.9 MONTHS twice-weekly Vd

Depth of response observed with once-weekly XPOVIO + Vd was significant versus twice-weekly Vd (p=0.0082)[1]



IMPROVEMENT IN ORR WAS OBSERVED ACROSS A VARIETY OF PATIENT SUBGROUPS[2]

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[1] XPOVIO (selinexor) package insert
[2] Grosicki et al. The Lancet. 2020.

Adverse Reactions in Patients with Multiple Myeloma Who Receive XVd[1]

- The most common adverse reactions (≥20%) in patients with multiple myeloma who receive XVd are fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, cataract and vomiting
- Grade 3-4 laboratory abnormalities (≥10%) are thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia

Full Prescribing Information and Medication Guide available at www.XPOVIO.com

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[1] XPOVIO (selinexor) package insert

Key Messaging for Expanded Indication in Multiple Myeloma

Unmet Need	In MM, treating with ***different mechanisms as early as possible*** may be ***vital for success***
Efficacy & Duration	Weekly XPOVIO + Vd conferred a rapid and sustained PFS benefit. And patients achieved a clinically significant durable response with once-weekly XPOVIO + Vd regardless of cytogenetics, renal impairment, or prior therapeutic exposure
Mechanism of Action	XPOVIO is the first and only FDA-approved oral XPO1 inhibitor that gets to the cell's nucleus which leads to cell cycle arrest and apoptosis in cancer cells • First new mechanism approved since 2016 for the treatment of MM in patients who received at least 1 prior therapy • XPOVIO has a strong synergistic effect with proteasome inhibitors, leading to cancer cell death
Dosing	The oral, once-weekly XPOVIO + once-weekly Vd combination offers a high-efficacy regimen while potentially reducing the burden for in-office Velcade® treatment
Safety	XPOVIO + Vd offers a manageable safety profile for a broad range of patients

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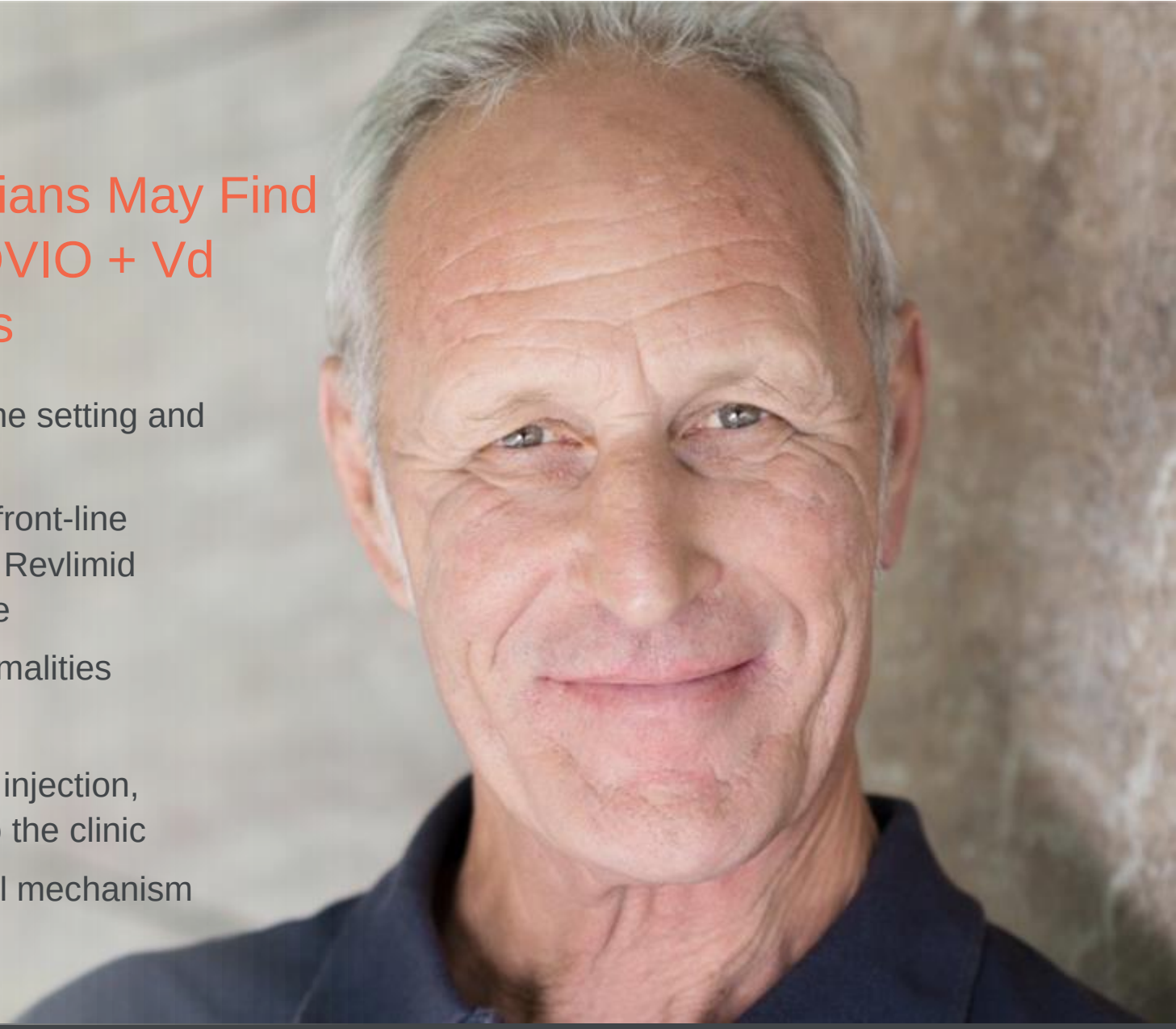
Specific Patient Types that Physicians May Find Particularly Appealing for the XPOVIO + Vd Regimen in the 2nd Line+ Settings

- Received Revlimid® and Darzalex® in the front-line setting and are Velcade®-naïve when they first relapse
- Received only a short course of Velcade® in the front-line setting prior to a stem cell transplant followed by Revlimid maintenance without receiving additional Velcade
- Have high-risk disease and/or cytogenetic abnormalities
- Have renal dysfunction
- Prefer a once weekly oral drug and once-weekly injection, rather than IV infusions or more frequent visits to the clinic
- Might benefit from a drug with a completely novel mechanism of action, synergistic with a proteasome inhibitor



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DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Commercial Strategy for XPOVIO in DLBCL

XPOVIO POSITIONING

- Position XPOVIO as a preferred DLBCL treatment option after two prior lines of therapy instead of traditional intravenous chemotherapy by educating physicians on the deep and durable efficacy achieved in clinical studies with oral, single-agent, novel, XPOVIO
- XPOVIO offers compelling efficacy with a manageable safety profile and is now:
  - **First** oral therapy approved for RR DLBCL
  - **First** single agent approved in any line of DLBCL treatment
  - **First** therapy a RR DLBCL patient can be taken at home

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Key Features of XPOVIO for the Treatment of Patients With RR DLBCL

Factors that influence treatment choice	Key features of XPOVIO
• Clinical efficacy	• 29% ORR[1] • 13% CR[1] • Clinically meaningful duration of response[1]
• Previous therapies / approaches	• Novel mechanism of action
• Subtype and histology	• Similar efficacy seen across both ABC and GCB patient sub-types
• Comorbidities • Functional status, age, frailty	Common adverse events do not include: • Peripheral neuropathy • Cardiac, liver or kidney toxicity • Opportunistic infections
• Patient preferences / logistical dynamics	• Oral route of administration taken only twice per week • Single agent, not combined with chemotherapy

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[1] XPOVIO (selinexor) package insert

PIPELINE AND SOLID TUMORS

Ongoing and Planned XPOVIO Company-Sponsored Studies in Hematologic Cancers

	Ongoing Hematologic Cancer Studies	Planned Hematologic Cancer Studies
MULTIPLE MYELOMA	• **STOMP** study evaluating XPOVIO in combination with backbone therapies in patients with previously treated multiple myeloma | **Phase 1b/2**	• **XPORT-MM-031** study evaluating XPOVIO in combination with pomalidomide and dexamethasone in patients with previously treated multiple myeloma | **Phase 3**
DLBCL	• **XPORT-DLBCL-030** study evaluating XPOVIO in combination with-gemcitabine-dexamethasone-platinum (R-GDP) | **Phase 2/3** • **XPORT-DLBCL-025** study evaluating XPOVIO in combination with backbone treatments or novel therapies in patients with relapsed or refractory DLBCL | **Phase 1/2**	
MYELOFIBROSIS	• **XPORT-MF-034** study in combination with ruxolitinib in treatment naïve patients | **Phase 1/2** • **XPORT-MF-035** study in previously treated patients | **Phase 2**	

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Ongoing and Potential Future XPOVIO Company-Sponsored Studies in Solid Tumors

	Current Solid Tumor Studies	Exploring Future Solid Tumor Studies
SARCOMA	• Dedifferentiated Liposarcoma: SEAL Study in patients with advanced unresectable disease | Phase 3	• **Sarcoma:** Combinations with other active drugs to be conduced through our CRADA partnership
GYNECOLOGICAL CANCER	• Endometrial: SIENDO Study in frontline maintenance setting (single agent vs. placebo) | Phase 3	• **Ovarian:** Resistant or refractory to platinum in combination with paclitaxel • **Endometrial and Ovarian:** Multiple arms and combinations
LUNG CANCER	• NSCLC: 2nd and 3rd line settings (KRAS mutant and wildtype) in combination with docetaxel | Phase 1	• **NSCLC:** 2nd line setting in combination with docetaxel • **NSCLC:** 1st line in combination with check-point inhibitors
BRAIN CANCER	• GBM: 1st and 2nd line settings with radiation + / - temozolomide, or lomustine | Phase 1/2	• **GBM:** Combinations with other active drugs to be conduced through our CRADA partnership
COLORECTAL	• CRC: 1-3 prior lines in combination with pembrolizumab | Phase 1	• **CRC:** 1st line setting in combination with FOLFOX and 2nd line in combination with FOLFIRI
MELANOMA		• **Melanoma:** 1st line in combination with pembrolizumab • **Melanoma:** Multiple arms and combinations

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Solid Tumor Update: SEAL Phase 3 Positive Top-Line Results

TOP-LINE PHASE 3 DATA

- Study met **primary endpoint** with significant increase in progression-free survival in patients with unresectable dedifferentiated liposarcoma following at least two prior therapies
- Hazard ratio=**0.70**; p=**0.023**
- Safety profile consistent with previous clinical studies with fewer hematologic and infectious adverse events as compared to selinexor studies in patients with multiple myeloma and diffuse large B-cell lymphoma
- Full data presented in an oral presentation at the Connective Tissue Oncology Society (CTOS) Annual Meeting on November 20, 2020

STRAGEGIC IMPLICATIONS

- Positive pivotal data in liposarcoma demonstrates XPOVIO's substantial potential across multiple solid tumors, representing a major advance for the development and commercial potential of XPOVIO in oncology
- Consistent with other, earlier stage positive results from ongoing XPOVIO studies in diseases such as endometrial cancer, GBM, melanoma, lung cancer, and others

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ADDITIONAL RECENT DEVELOPMENTS AND NEXT STEPS

Status Update Across Potential Select Near-Term Opportunities

A focused and targeted approach towards building a "portfolio in a pill"

Phase 3 SIENDO Study in patients with endometrial cancer

- Passed planned interim futility analysis: Data and Safety Monitoring Board has recommended study should continue without the need for adding additional patients to the trial or amending the study protocol
- Top-line data expected in second half of 2021

Multiple myeloma in Europe (STORM, BOSTON)

- Based on ongoing discussions with CHMP, Karyopharm now expects a final opinion on the MAA requesting conditional approval for patients with heavily pretreated multiple myeloma by February 2021
- Following receipt of CHMP's opinion, we now expect to submit a second MAA based on the data from the BOSTON study shortly thereafter

Dedifferentiated liposarcoma (SEAL)

- Given the positive results from the SEAL study, Karyopharm is currently evaluating the optimal approach and next steps towards making XPOVIO available to patients with dedifferentiated liposarcoma, including cost, commercial potential and regulatory strategy
- We no longer expect to file an NDA in the first quarter of 2021 and will provide an update regarding our approach and timelines following our evaluation

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Current Partnerships

Commercial partnerships to serve global markets

Antengene Corporation

Licensing partner for selinexor, eltanexor, verdinexor and KPT-9274 in China, South Korea, Taiwan, Australia and other Asia-Pacific markets, with the exception of Japan

Neopharm Group

Exclusive distribution agreement for the commercialization of XPOVIO in Israel and the Palestinian Authority

FORUS Therapeutics, Inc.

Exclusive distribution agreement for the commercialization of XPOVIO in Canada

Europe, Japan and Other Key Markets

Evaluating potential collaboration arrangements with commercial partners; analyzing potential for Karyopharm to commercialize in select European markets

KARYOPHARM IS COMMITTED TO WORKING ACROSS THE GLOBE TO BRING NOVEL THERAPIES TO PATIENTS

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Balance Sheet and Financial Guidance

Balance sheet	December 31, 2020	December 31, 2019
Cash, Cash Equivalents, Restricted Cash and Investments	$277M[1]	$265.8M

Cash runway expected to be sufficient to fund planned operations into late 2022

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[1] Preliminary unaudited estimate

Karyopharm Near and Medium-Term Corporate Priorities

NEXT 1-2 YEARS
(2021-2022)

- **Increasing impact on the lives of patients battling cancer**
- U.S. launch of XPOVIO and expansion in 2nd line+ multiple myeloma and subsequent significant increase in annual sales
  - Increase in sales largely driven by earlier use (5x more patients) and longer duration of treatment in patients with multiple myeloma (3x longer)
- Initial approval(s) and commercial launch of XPOVIO in Europe (based on STORM and BOSTON studies) and other international markets[1]
- Read-out of Phase 3 SIENDO study in endometrial cancer (2H 2021)
- Continued clinical development for XPOVIO, eltanexor, and KPT-9274 in additional cancer indications

NEXT 3-5 YEARS
(2023-2025)

- **Increasing impact on the lives of patients battling cancer**
- Additional indication approvals for XPOVIO, including in solid tumors, across U.S. and international markets[1]
- Meaningful revenue contributions from royalties and milestones on international XPOVIO sales[1]
- Continued pipeline expansion for XPOVIO, eltanexor, and KPT-9274
- XPO1 inhibition established as a core therapeutic approach in cancer therapy

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[1] Subject to regulatory submission and/or approval(s)

QUESTIONS?

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