Karyopharm® Therapeutics

A Commercial-Stage Pharmaceutical Company Pioneering Novel Cancer Therapies

April 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 guidance on its 2021 non-GAAP research and development and selling, general and administrative expenses and cash runway; expectations and plans relating to XPOVIO for the treatment of patients with relapsed or refractory multiple myeloma in the U.S. or the European Union or relapsed or refractory diffuse large B-cell lymphoma in the U.S.; commercialization of XPOVIO or any of its product candidates and the commercial performance of XPOVIO/NEXPOVIO; beliefs about the U.S. market size for XPOVIO, submissions to, and the review and potential approval of selinexor by, U.S. and foreign 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 product 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 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 product candidates will continue. Further, there can be no guarantee that any positive developments in the development or commercialization of Karyopharm's product 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 agreements; Karyopharm's ability to obtain and maintain requisite regulatory approvals and 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 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.

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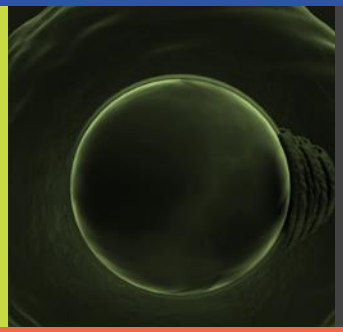
Karyopharm at a Glance

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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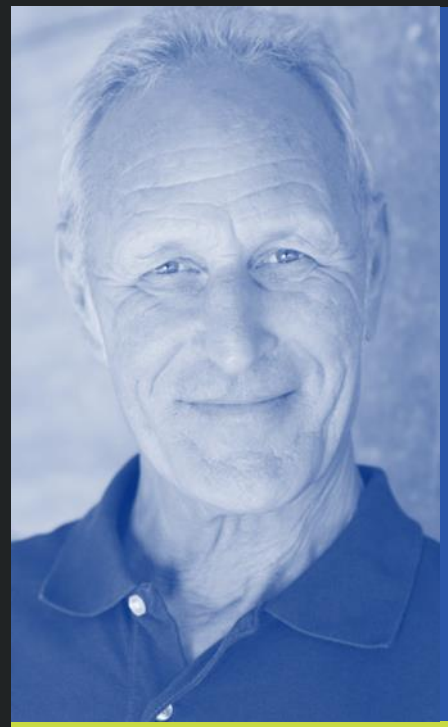
Karyopharm at a Glance

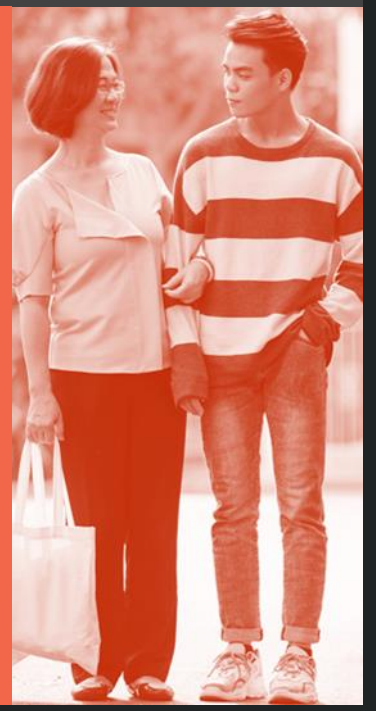


XPOVIO also received accelerated approval in June 2020 for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

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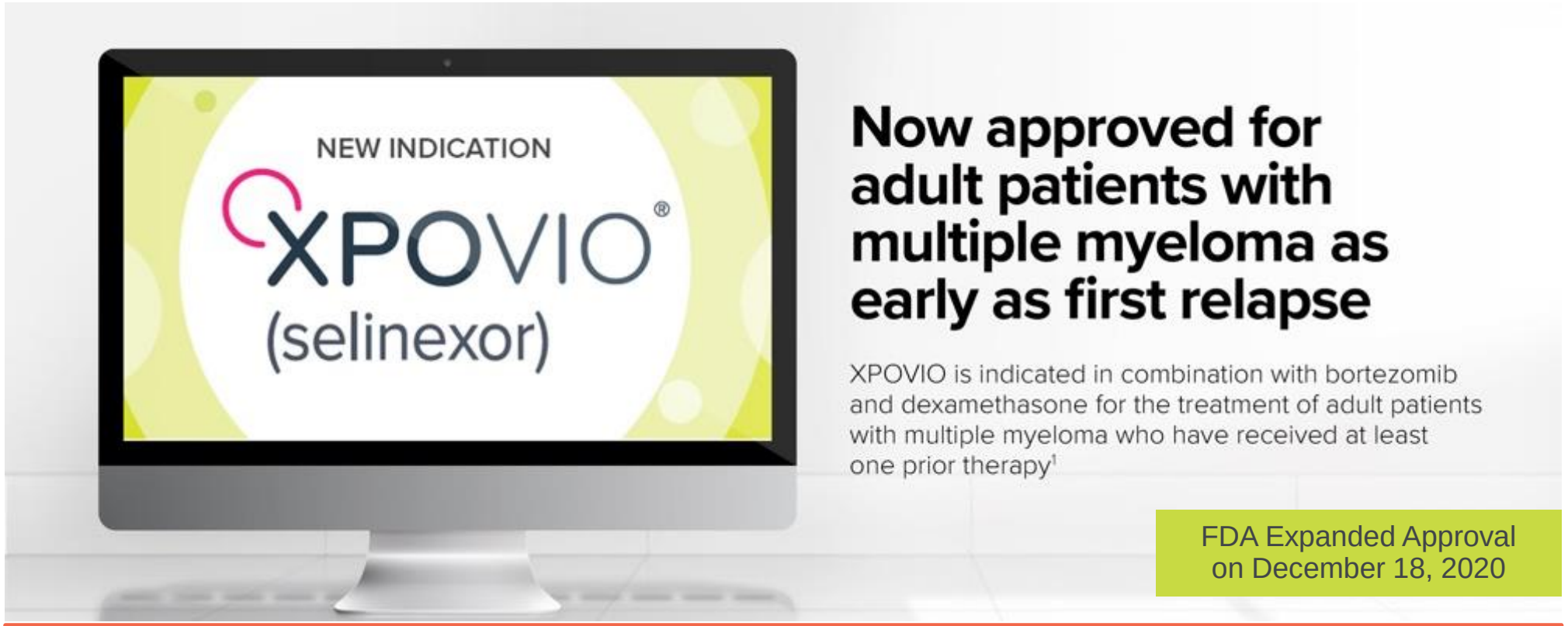
XPOVIO Now Approved In Significantly Expanded Multiple Myeloma (MM) Patient Population



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

Q4 2020 and Recent Achievements Help Position Karyopharm For Significant Future Growth

Commercial Update

- **Expanded U.S. approval** of XPOVIO® and commercial launch (Dec 18, 2020)
- Q4 and full year 2020 XPOVIO net sales of **$20.2M** and **$76.2M**, respectively
- National Comprehensive Cancer Network® adds **three XPOVIO treatment regimens** to its clinical practice guidelines for multiple myeloma
- **>170** and **>700 new** physicians / accounts prescribed XPOVIO in Q4 and full year 2020, respectively

Pipeline / Clinical Data Update

- **Conditional Marketing Authorization** for NEXPOVIO® (selinexor) in Europe granted based on STORM study (multiple myeloma)
- **Regulatory approval** in Israel
- **Positive Phase 3 BOSTON study** results published in the *Lancet* (multiple myeloma)
- **Positive Phase 3 Seal study** results presented at CTOS annual meeting (liposarcoma)
- **Phase 3 SIENDO study** passes planned interim futility analysis (endometrial cancer)
- **1st patient dosed** in Phase 3 confirmatory trial in DLBCL (XPORT-DLBCL-30)

Corporate Development and Balance Sheet

- Q4 and full year 2020 license revenue of **$14.9M** and $**31.9M**, respectively
- Ended Q4 2020 with **$276.7M** in cash, cash equivalents, restricted cash and investments
- Cash runway expected to be sufficient to fund planned operations into **late 2022**

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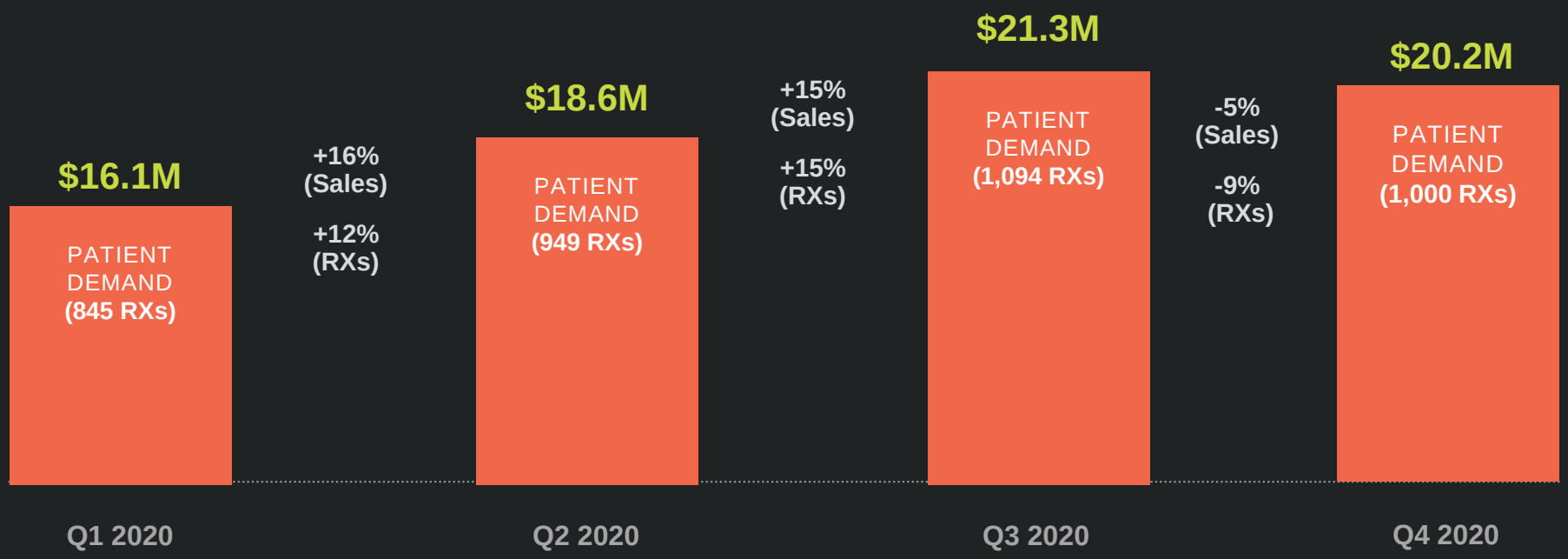
XPOVIO 2020 Quarterly Net Product Sales and Prescription (RX) Trends



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Update on Q4 2020 and Recent Sales Trends

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 and January following declines in October and November of 2020

- Positive sales momentum seen in December 2020 and January 2021 following NCCN guideline update adding three XPOVIO regimens to its treatment recommendations and the expanded XPOVIO FDA approval granted on December 18th
- Increase in estimated new patient starts seen in December and January as compared to October and November

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Status Update on Commercial Expansion in Europe

1. Conditional Marketing Authorization from the European Commission granted on March 29, 2021

- NEXPOVIO is indicated in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy
- EC marketing authorization follows positive CHMP opinion issued on January 29, 2021
- Karyopharm to submit second regulatory filing based on data from the confirmatory Phase 3 BOSTON study by April 2021

2. Selinexor added to European treatment guidelines in November 2020

- Multiple myeloma treatment guidelines developed by the European Hematology Association (EHA) and European Society for Medical Oncology (ESMO) added SVd* as a treatment option in the second line setting and Sd** for patients with triple-class refractory disease

3. Advancing partnership discussions for international markets

- Evaluating potential collaboration strategies with commercial partners for Europe and Japan
- Largest revenue opportunity in Europe to come following potential approval based on data from the BOSTON study which could occur before the end of 2021[1]

*Selinexor, Velcade®, dexamethasone
** Selinexor, dexamethasone

[1] Subject to regulatory submission and approval

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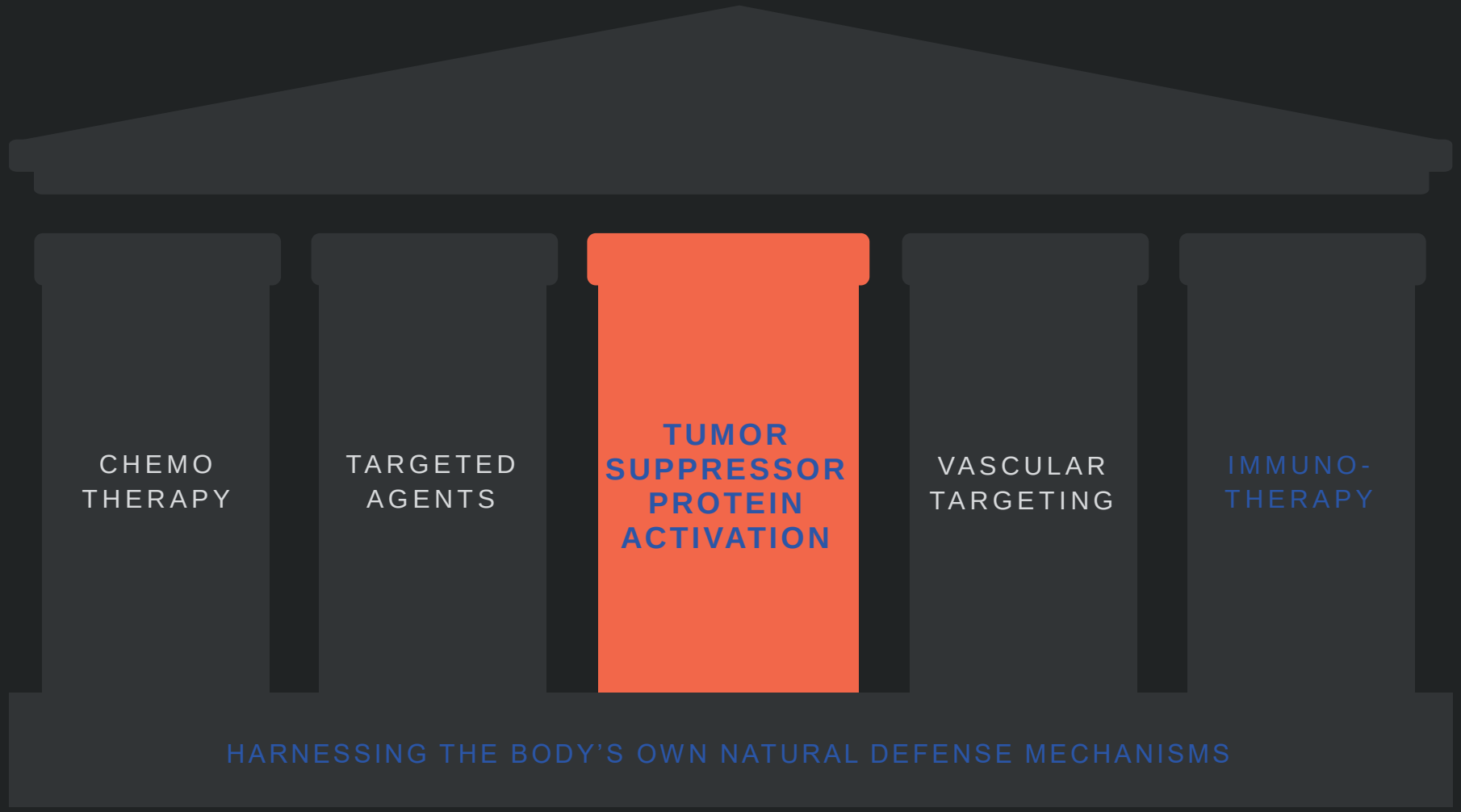
INNOVATIVE APPROACH TO TARGETING CANCER

Core Pillars of Cancer Drug Therapy



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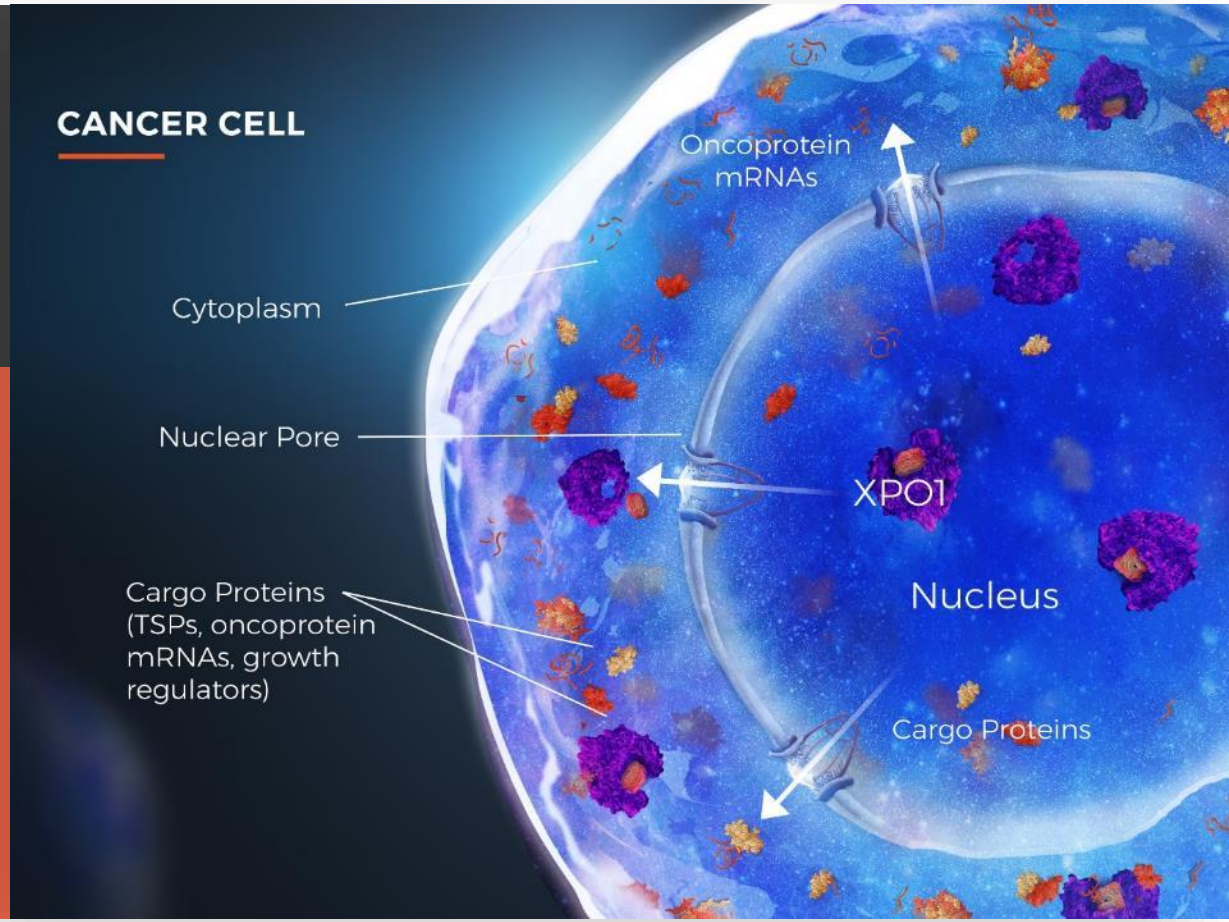
XPOVIO® (selinexor) / SINE Mechanism of Action: Inhibition of XPO1[1-4]

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

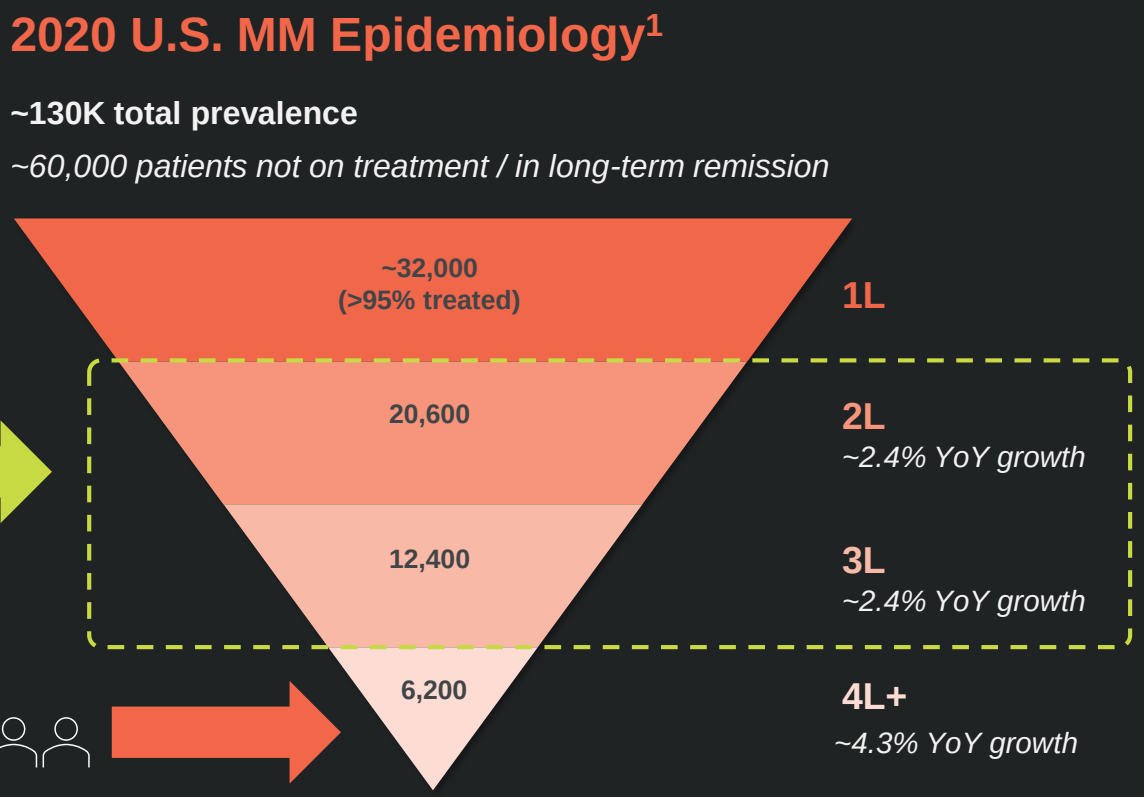
MULTIPLE MYELOMA

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**

[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.

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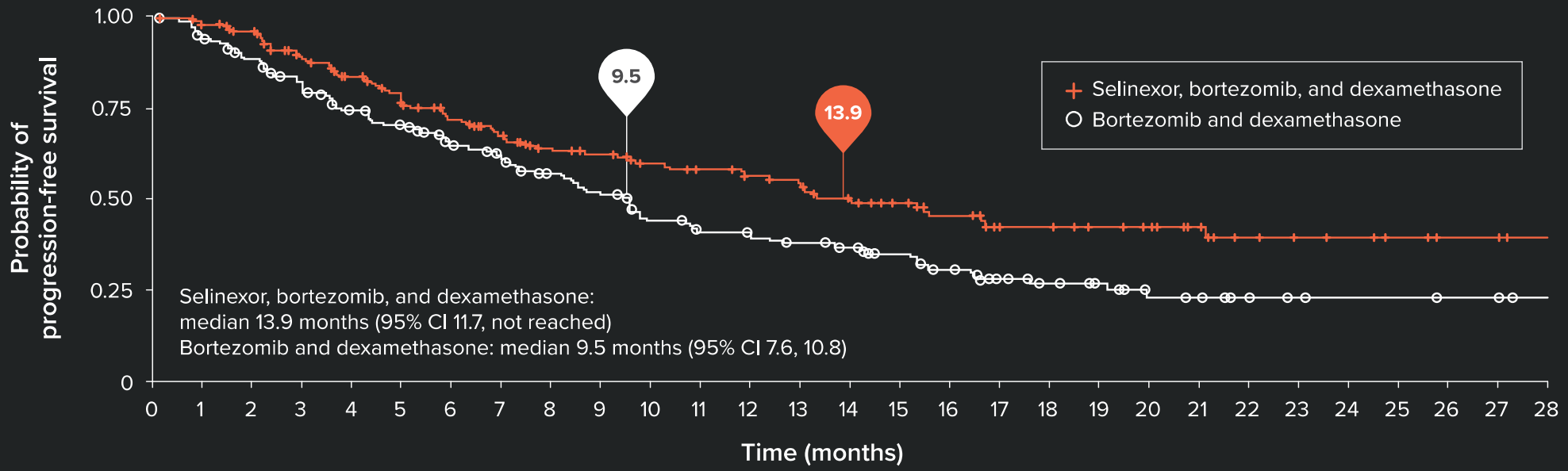
Progression Free Survival (PFS) Significantly Longer with XVd Compared to Vd

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

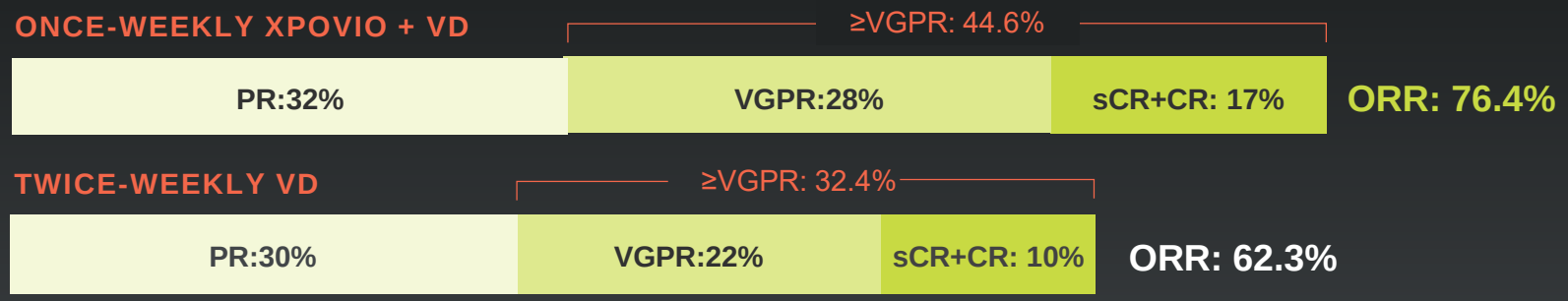
MEDIAN DURATION OF RESPONSE[1]

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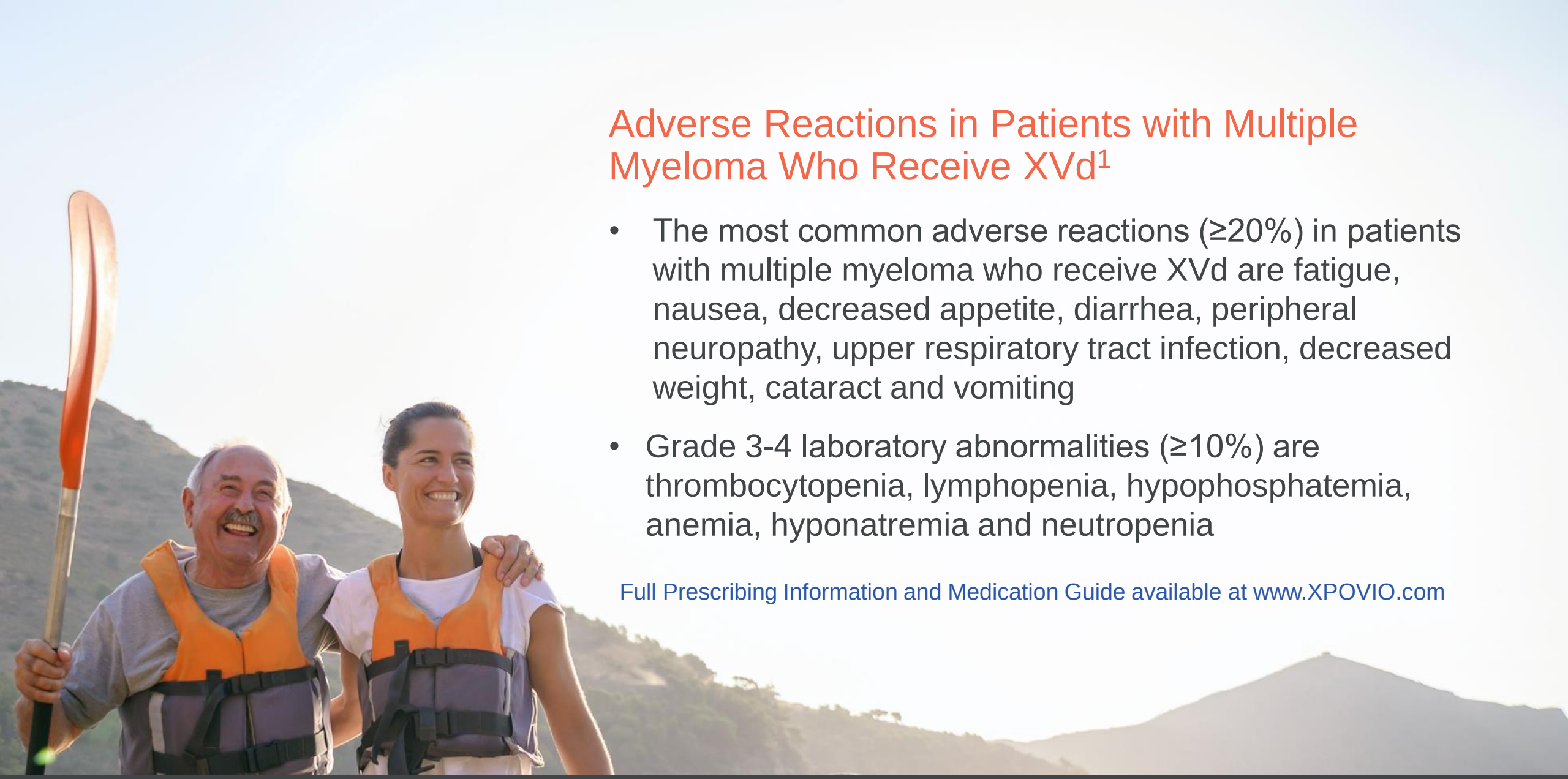
[1] XPOVIO (selinexor) package insert [2] Grosicki et al. The Lancet. 2020.



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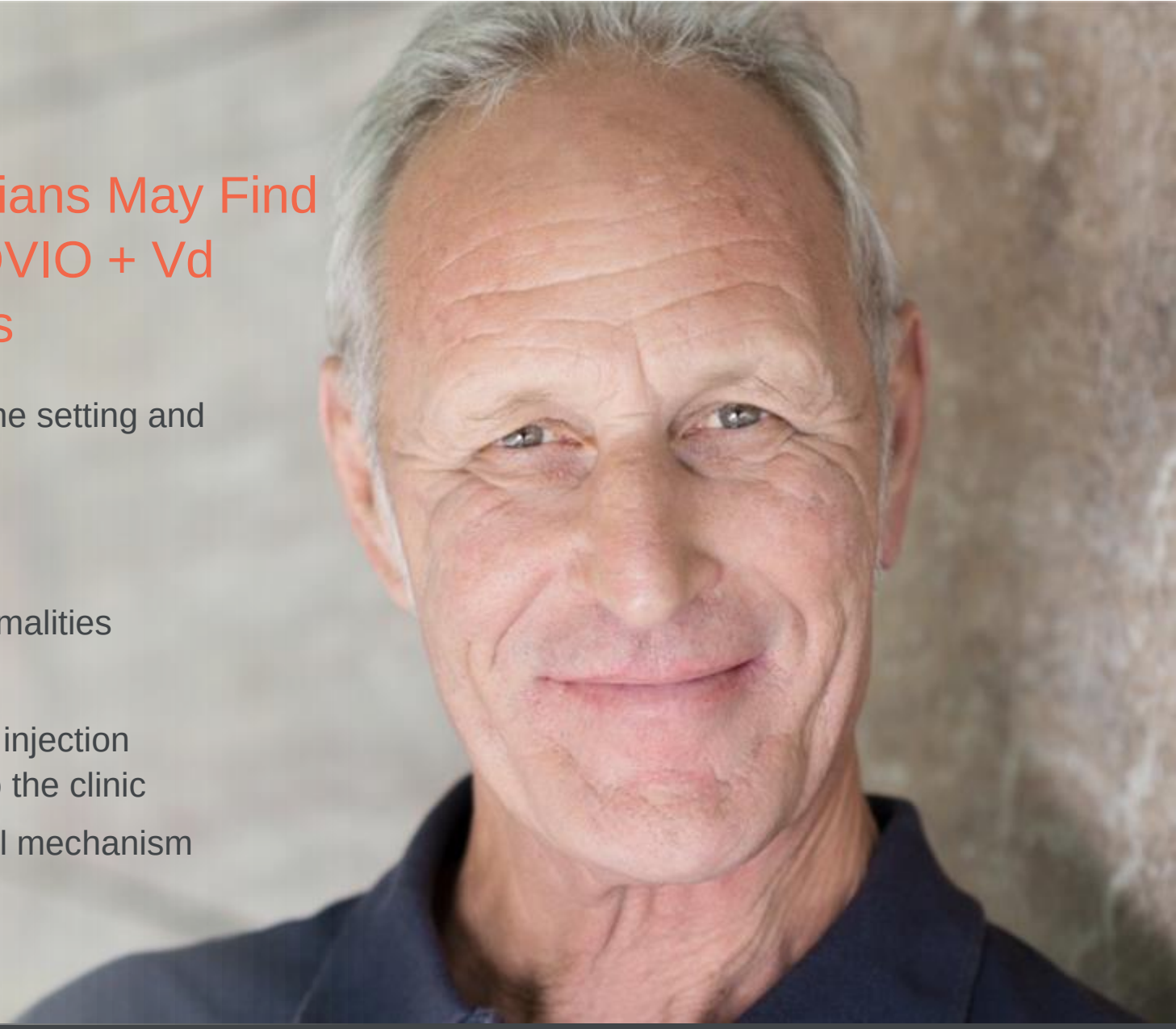
Specific Patient Types that Physicians May Find Particularly Appealing for the XPOVIO + Vd Regimen in the 2nd Line+ Settings

- Received Revlimid® and Darzalex® in the front-line setting and are Velcade®-naïve following first relapse
- Received only a short course of Velcade® in the front-line setting prior to stem cell transplant
- 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 the 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 take 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

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**

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[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**			

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Karyopharm's Novel Pipeline | Eltanexor, KPT-9274 and Verdinexor

ADDITIONAL ONCOLOGY PROGRAMS - ELTANEXOR AND KPT-9274	PHASE 1	PHASE 2	PHASE 3
Myelodysplastic Syndromes (MDS) (single agent or in combination with hypomethylating agents)[1] Drug: **Eltanexor**			
Colorectal Cancer (CRC) and Prostate Cancer (PrC) Drug: **Eltanexor**			
Solid Tumors & AML Drug: **KPT-9274**			

INFECTIOUS DISEASES & AUTOIMMUNE DISORDERS - VERDINEXOR	PHASE 1	PHASE 2	PHASE 3
Healthy Human Volunteers			
Systemic Lupus Erythematosus (SLE) | **VALOR-SLE-705**[2]			
Severe Influenza, Respiratory Syncytial Virus (RSV), HIV Inflammation, Spinal Cord Injury[2]			

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[1] Study expected to start in 2021. [2] Study start pending submission and acceptance of IND.

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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Potential Endometrial Cancer Opportunity for Selinexor

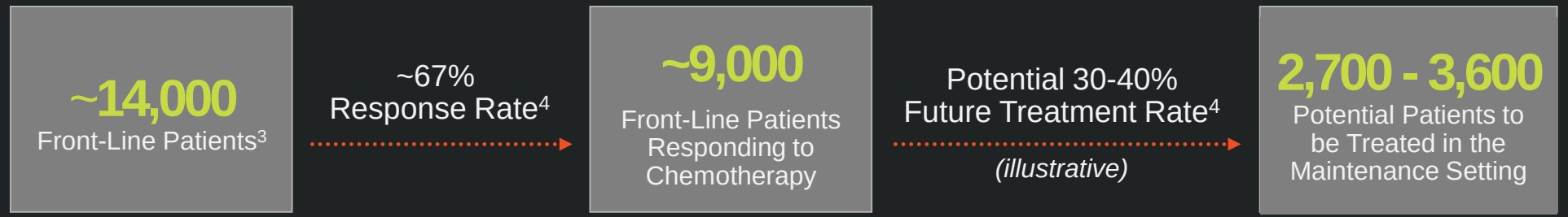
Overview and Epidemiology (US)

- 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)

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

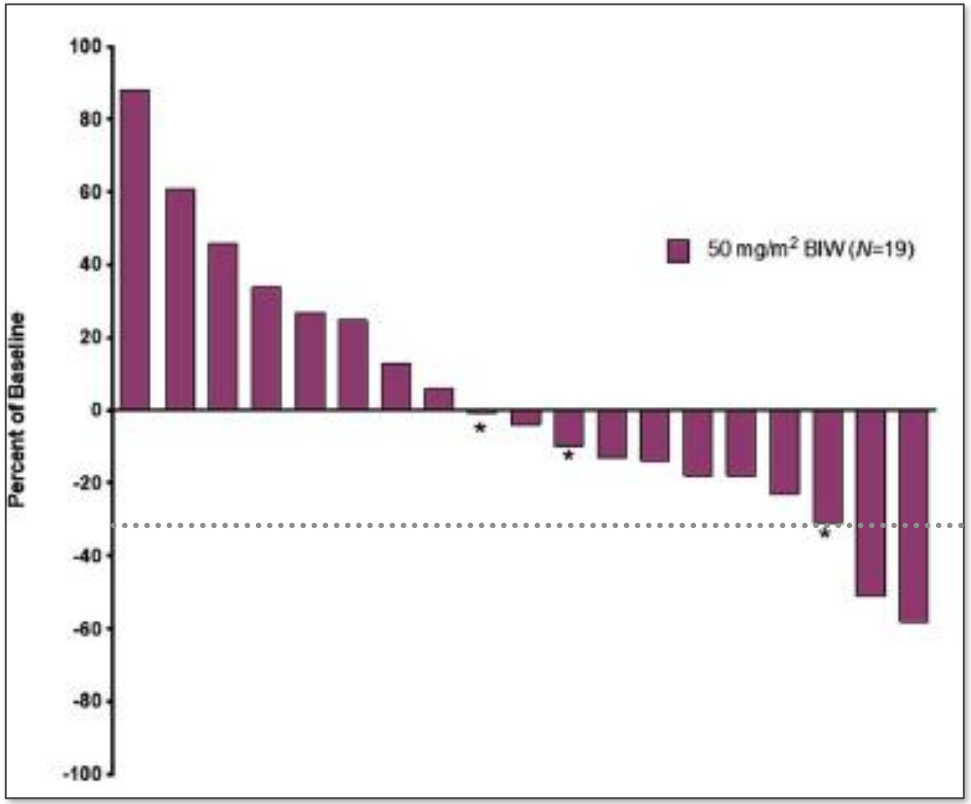
Baseline Patient Characteristics	
# of endometrial cancer patients in study	23
Previous lines of therapy (median, range)	2 (1-5)
Previous platinum agent Previous taxane	96% 100%
Endpoints	
Disease Control Rate (patients with PR or SD) Response Rate (confirmed PRs)	35% 9%

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, 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

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SIENDO Study Design

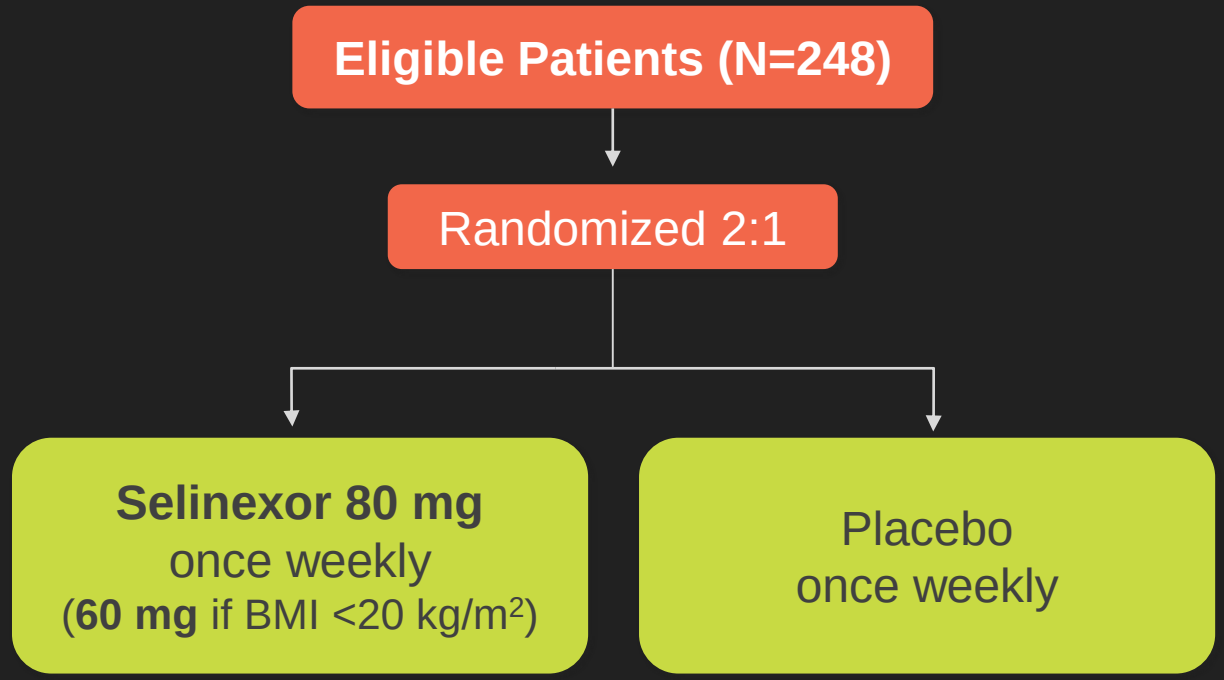
Eligibility

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

- PFS from time of randomization until death or PD as determined by Investigator



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

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ADDITIONAL HIGHLIGHTS AND NEXT STEPS

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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Q4 and Full Year 2020 Financial Results

Statement of Operations	Three Months Ended December 31st		Twelve Months Ended December 31st	
	2020	2019	2020	2019
Total Revenue	$35.1M	$18.1M	$108.1M	$40.9M
XPOVIO Net Sales	$20.2M	$17.7M	$76.2M	$30.5M
License and other Revenue	$14.9M	$0.4M	$31.9M	$10.4M
Total Operating Expenses	$72.2M	$61.4M	$279.9M	$230.2M
Cost of Sales	$1.1M	$1.4M	$2.7M	$2.4M
Research and Development Expenses	$37.2M	$31.6M	$150.8M	$122.3M
Selling, General & Administrative Expenses	$33.9M	$28.4M	$126.4M	$105.4M
Net Loss	$43.4M ($0.59 per share)	$48.6M ($0.76 per share)	$196.3M ($2.72 per share)	$199.6M ($3.22 per share)

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Balance Sheet and Financial Guidance

Balance sheet	December 31, 2020	December 31, 2019
Cash, Cash Equivalents, Restricted Cash and Investments	$276.7M	$265.8M

- **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.

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Numerous Expected Key Milestones in 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 key medical meetings
6. Continued, increased U.S. XPOVIO sales

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

APPENDIX: CLINICAL DATA

Overview of Efficacy Data for Accelerated Approval of XPOVIO (n=83)[1]

25.3% Overall Response Rate (ORR)

INCLUDING

1 Stringent complete response

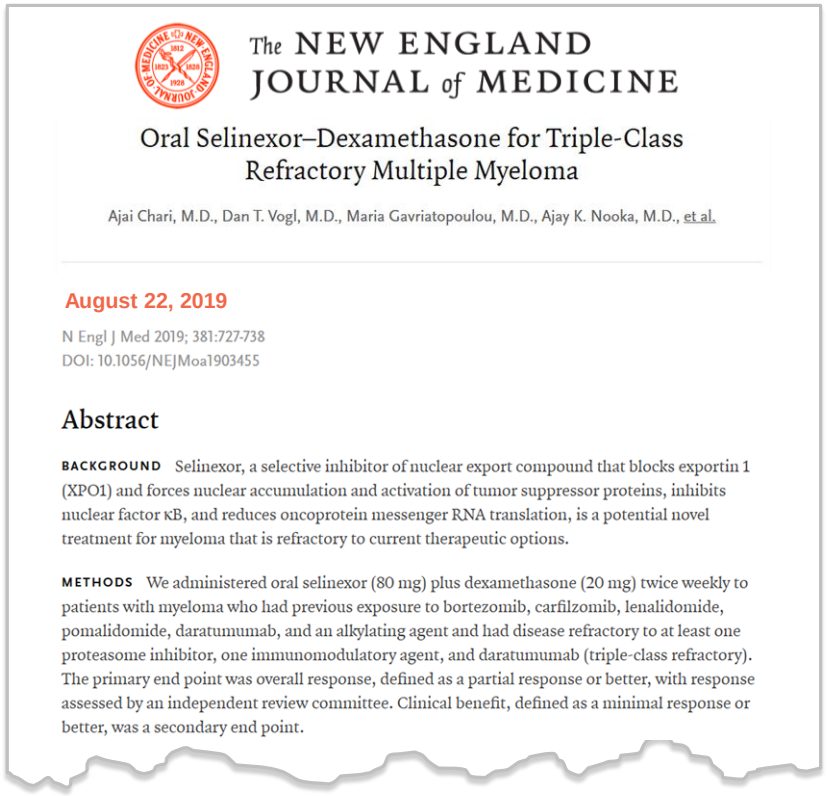
0 Complete responses

4 Very good partial responses

16 Partial responses

- Median time to response: **4** weeks
- Median duration of response: **3.8** months

Full STORM results from all 122 patients published in NEJM



The NEW ENGLAND JOURNAL of MEDICINE

Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma

Ajai Chari, M.D., Dan T. Vogl, M.D., Maria Gavriatopoulou, M.D., Ajay K. Nooka, M.D., et al.

August 22, 2019

N Engl J Med 2019; 381:727-738
DOI: 10.1056/NEJMoa1903455

Abstract

BACKGROUND Selinexor, a selective inhibitor of nuclear export compound that blocks exportin 1 (XPO1) and forces nuclear accumulation and activation of tumor suppressor proteins, inhibits nuclear factor κB, and reduces oncoprotein messenger RNA translation, is a potential novel treatment for myeloma that is refractory to current therapeutic options.

METHODS We administered oral selinexor (80 mg) plus dexamethasone (20 mg) twice weekly to patients with myeloma who had previous exposure to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and an alkylating agent and had disease refractory to at least one proteasome inhibitor, one immunomodulatory agent, and daratumumab (triple-class refractory). The primary end point was overall response, defined as a partial response or better, with response assessed by an independent review committee. Clinical benefit, defined as a minimal response or better, was a secondary end point.

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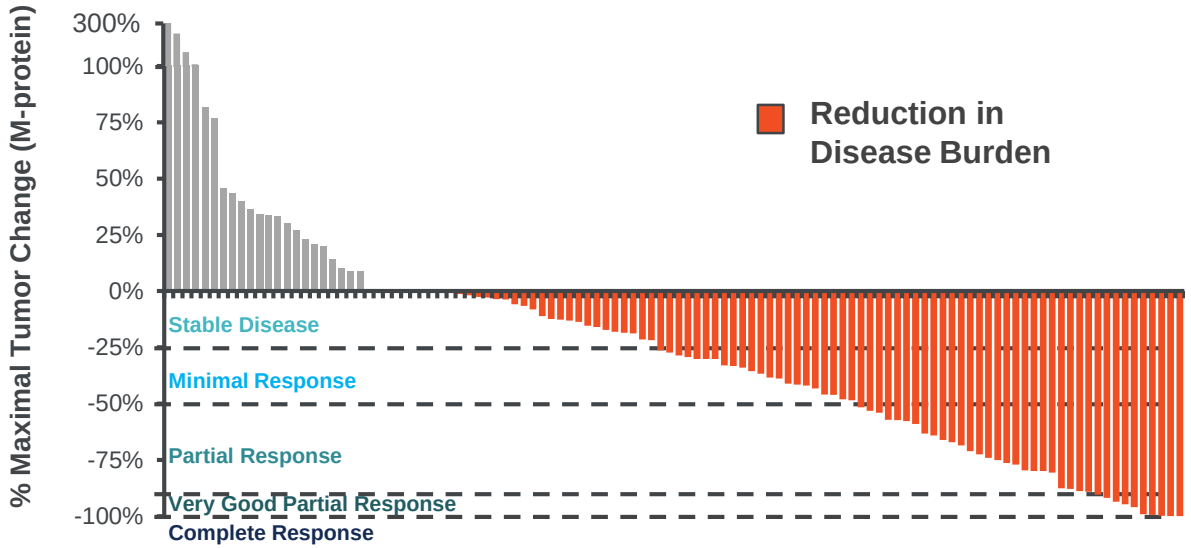
[1] XPOVIO (selinexor) package insert

Additional Efficacy Data from Part 2 of STORM (n=122)[1]

Change in M-Protein Levels[2]

71% of patients had a reduction in disease burden



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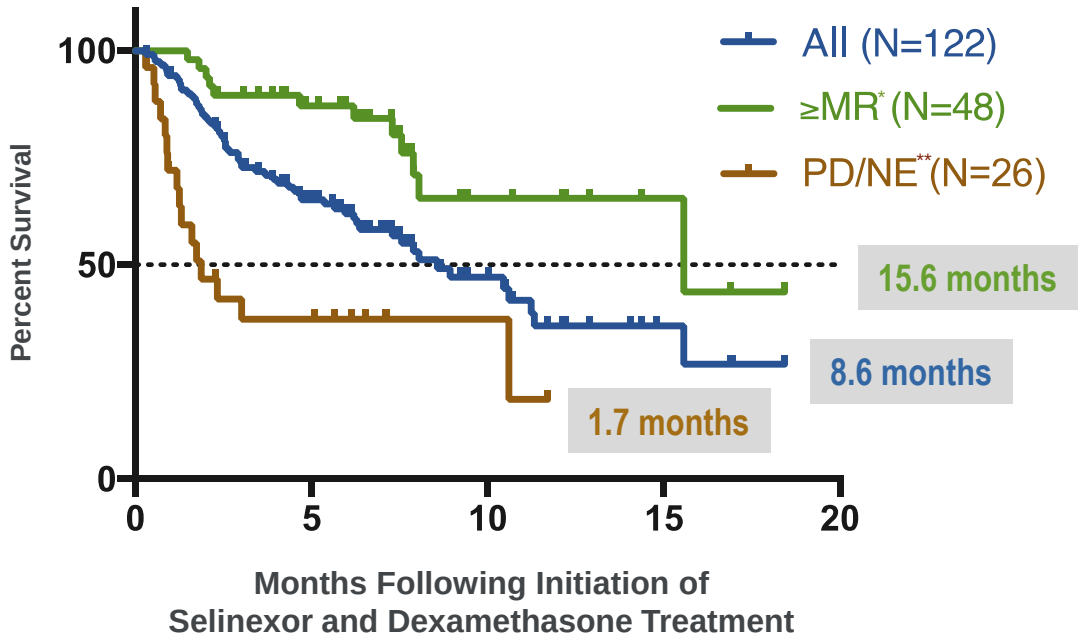
[1] The accelerated approval of XPOVIO was based upon the efficacy and safety in a prespecified subgroup analysis of the 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, as the benefit-risk ratio appeared to be greater in this more heavily pretreated population than in the overall trial population. [2] Selinexor ODAC Presentation, February 2019

Additional Efficacy Data from Part 2 of STORM (n=122)[1]

Overall Survival by Group[2]



* ≥MR = Patients had a minor response or better; at least a 25% decrease in M protein
** PD/NE = Patients had progressive disease or disease not evaluable

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[1] The accelerated approval of XPOVIO was based upon the efficacy and safety in a prespecified subgroup analysis of the 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, as the benefit-risk ratio appeared to be greater in this more heavily pretreated population than in the overall trial population [2] Chari A, et al. New England Journal of Medicine 2019.

Overview of Safety Data from STORM

- The most common adverse reactions (≥20%) in patients with multiple myeloma who receive Xd (XPOVIO and dexamethasone) are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea and upper respiratory tract infection
- In the STORM trial, fatal adverse reactions occurred in 9% of patients. Serious adverse reactions occurred in 58% of patients. Treatment discontinuation rate due to adverse reactions was 27%.

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

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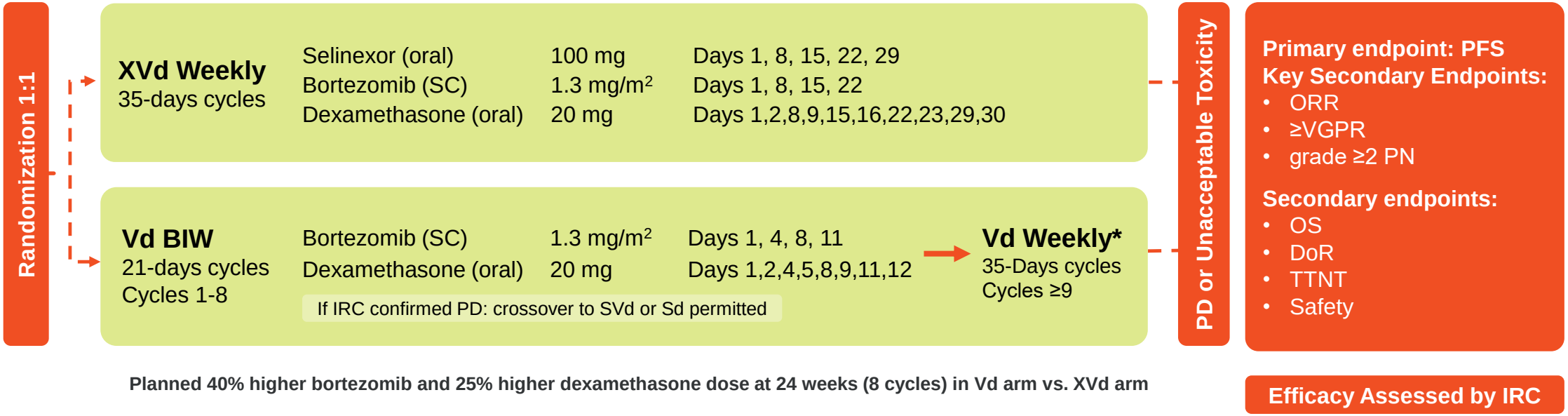
[1] XPOVIO (selinexor) package insert

BOSTON Study: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with Multiple Myeloma who Had Received 1-3 Prior Therapies



Planned 40% higher bortezomib and 25% higher dexamethasone dose at 24 weeks (8 cycles) in Vd arm vs. XVd arm

CR= complete response, DoR = duration of response, IMWG = International Myeloma Working Group, IRC = Independent Review Committee, OS = overall survival, PD = progressive disease, PFS = progression free survival, PR = partial response, PN = peripheral neuropathy, sCR = stringent complete response, TTNT = time to next therapy, VGPR = very good partial response. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments.

*Vd weekly dosing and schedule for cycles≥ 9 as per SVd arm description.

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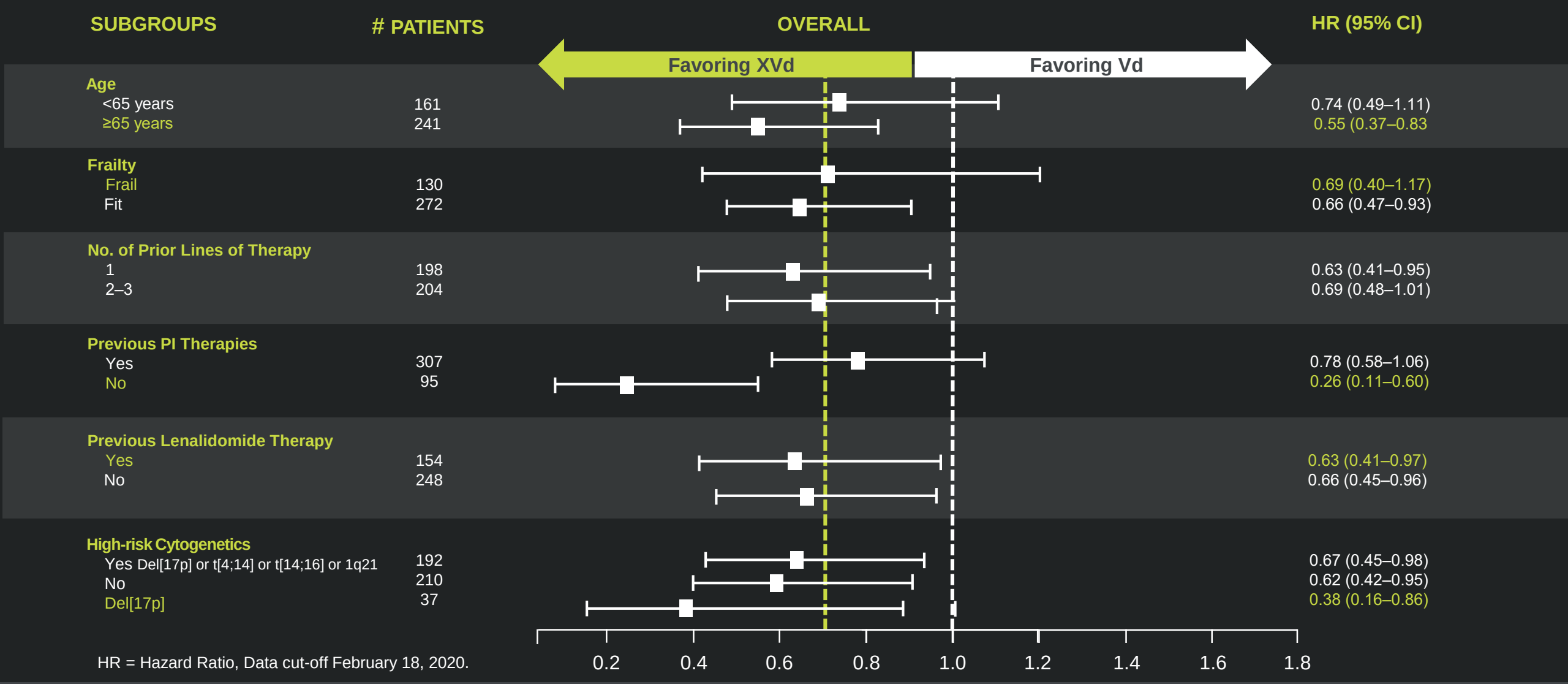
Consistent PFS Benefit for XVd Across Subgroups



HR = Hazard Ratio, Data cut-off February 18, 2020.

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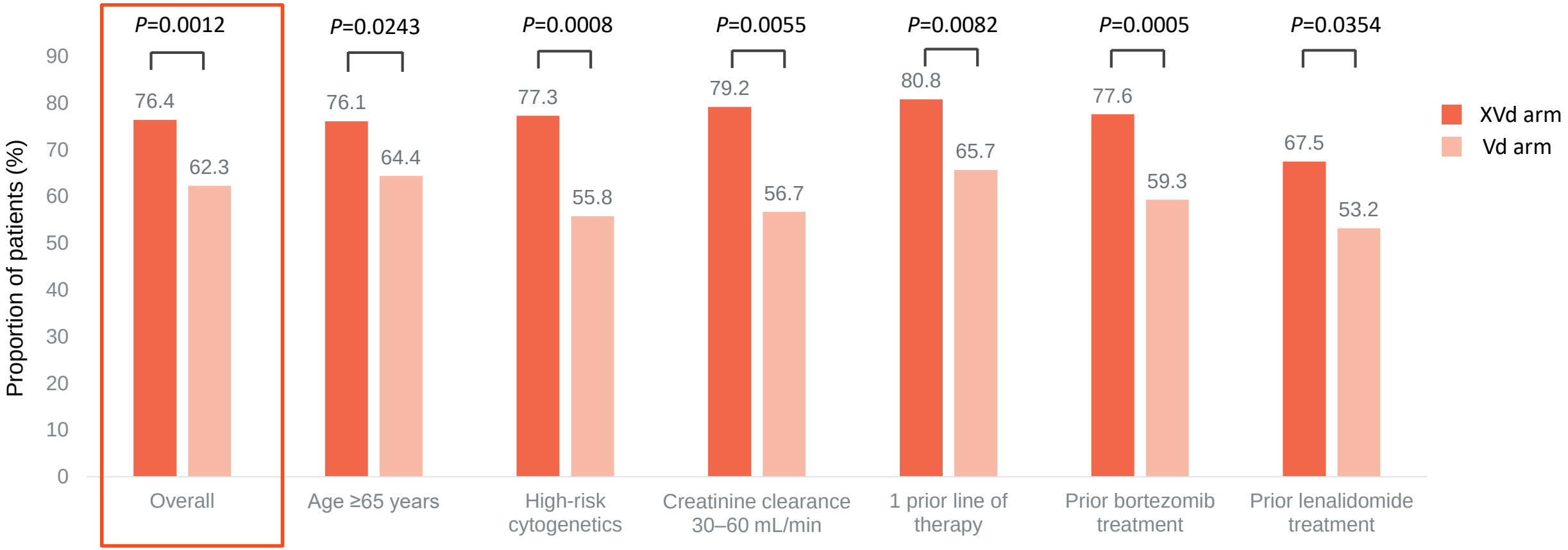
Source: Dimopoulos M, et al. ASCO 2020. Abstract 8501.

XVd Was Associated With a Significantly Higher ORR Overall and Across Patient Subgroups



One-sided P values for the Cochran-Mantel-Haenszel Test based on unstratified model. Data cut-off February 18, 2020.
ORR = Overall Response, based on Independent Review Committee's (IRC) response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet Oncology 2016).
All changes in MM disease assessments were based on baseline MM disease assessments.

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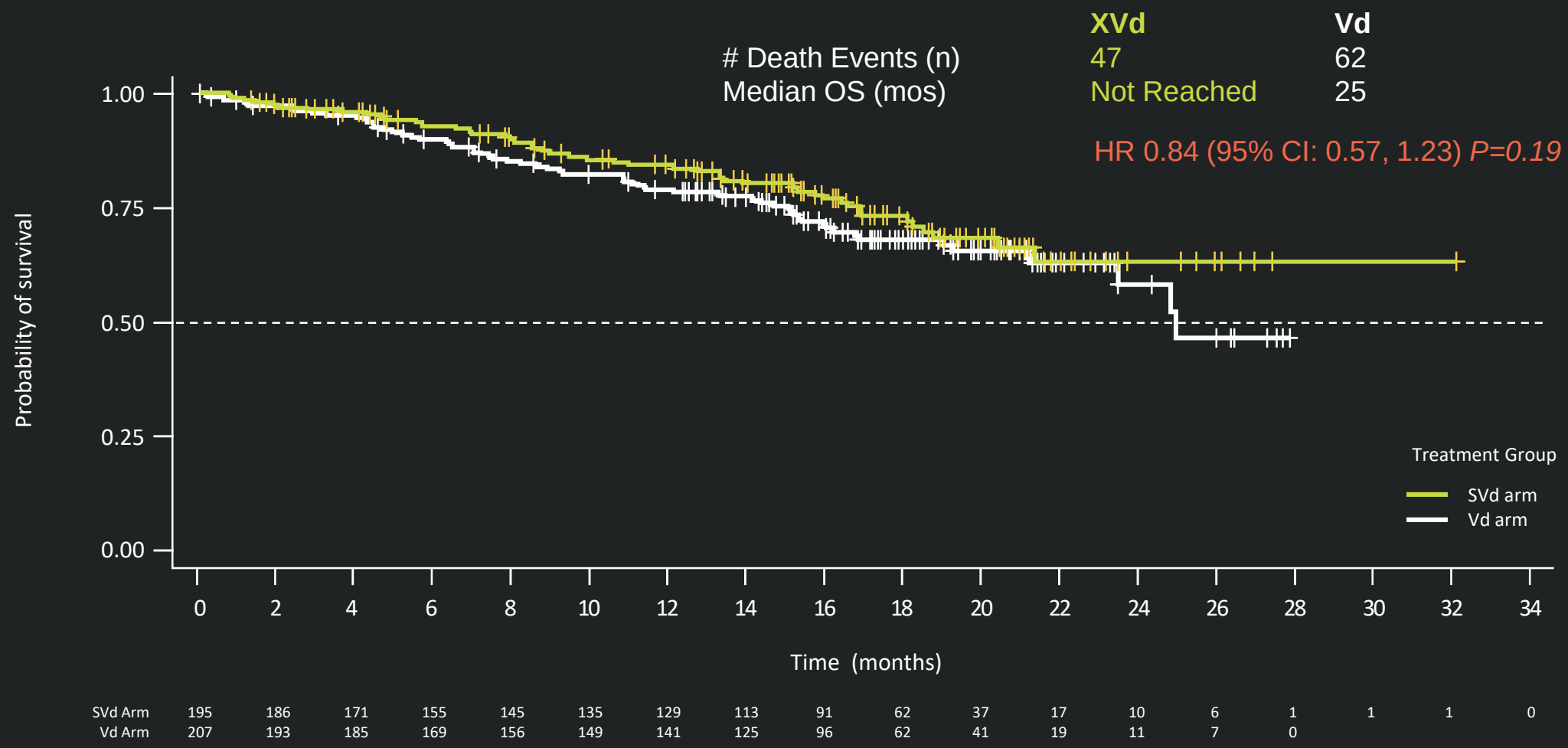
Source: Dimopoulos M, et al. ASCO 2020. Abstract 8501.

Overall Survival Interim Analysis (109 Deaths [27%])



OS = Overall Survival, Data cut-off February 18, 2020.

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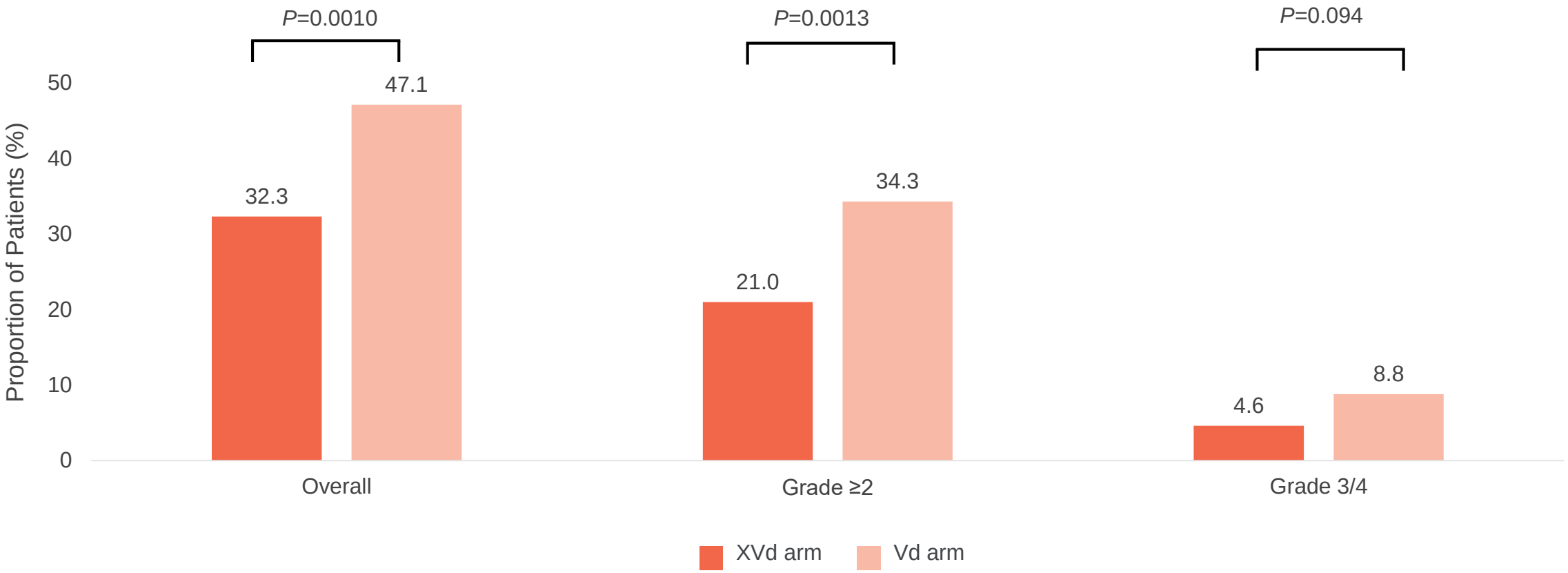
Source: Dimopoulos M, et al. ASCO 2020. Abstract 8501.

Peripheral Neuropathy Rates were Significantly Lower with XVd than with Vd



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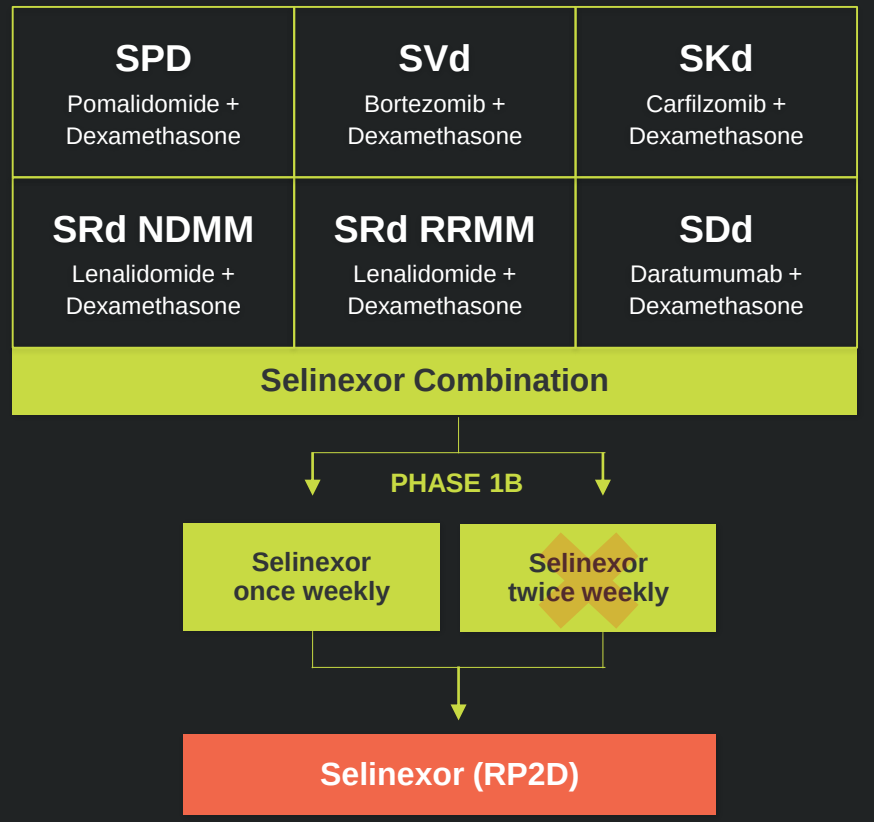
Source: Dimopoulos M, et al. ASCO 2020. Abstract 8501.

STOMP: Study Overview & Objectives

Selinexor and backbone Treatments of multiple Myeloma Patients (STOMP): Multi-center, open-label, dose escalation (Phase 1) and expansion (Phase 2) study to assess the MTD, efficacy, and safety of selinexor in patients with RRMM



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Note: MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; NDMM, newly diagnosed multiple myeloma.

Additional XPOVIO Triplet Regimens Indicate Additive or Synergistic Activity Compared to Benchmark Doublet Regimens

Selinexor is currently being studied in the ongoing STOMP Phase 1b/2 trial evaluating selinexor and low-dose dexamethasone in combination with one of several standard approved myeloma therapies in patients with relapsed or refractory multiple myeloma

STOMP TRIAL			BENCHMARK DATA	
STOMP Triplet Regimen	**# of Patients Treated to Date**	**Efficacy Data**	**Benchmark Regimen**	**Efficacy Data**
Selinexor + Kyprolis + dex	24 (median 3 lines of prior therapy)	ORR = 75%[1]	Kyprolis + dex	ORR = 23%[5]
Selinexor + Darzalex + dex	30 (Darzalex-naïve)	ORR = 73%[2] PFS = 12.5 months[2]	Darzalex	ORR = 29%[6] PFS = 3.7 months[6]
Selinexor + Pomalyst + dex	60 (Pomalyst–naïve or non-refractory)	ORR = 54% (all pts)[3] ORR = 60% (pts dosed at RP2D)[3] PFS = 12.3 months[3]	Pomalyst + dex	ORR = 29%[7] PFS = 3.6 months[7]
Selinexor + Revlimid + dex	12 (Revlimid-naïve)	ORR = 92%[4]	Revlimid + dex	ORR = 67%[8]

Note: The STOMP study does not include any arms studying current myeloma backbone therapies without the combination of selinexor. The purpose of displaying the "Benchmark" data above is to highlight that the clinical results from STOMP reported to date strongly support ongoing / additional clinical investigation of selinexor in combination regimens.

In December 2020, the National Comprehensive Cancer Network® (NCCN) added three different XPOVIO combination regimens (Velcade®, Pomalyst® and Darzalex®) to its Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for previously treated multiple myeloma

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[1] Gasparetto C, et al. ASH 2020. Abstract 1366. [2] Gasparetto C, et al. ASCO 2020. Abstract 8510. [3] Chen C, et al. ASH 2020. Abstract 726. [4] White D, et al. ASH 2020. Abstract 1393. [5] Kyprolis Package Insert; Study PX-171-003 A1 [6] Lonial et al. Lancet 2016. [7] Pomalyst Package Insert. [8] Stewart et al. NEJM 2015. [9] Revlimid® (lenalidomide), Pomalyst® (pomalidomide), Velcade® (bortezomib), Kyprolis® (carfilzomib) or Darzalex® (daratumumab).

SADAL: A Phase 2b Study In DLBCL

Relapsed or Refractory or Transformed DLBCL

- Study included patients with at least two prior multi-agent therapies and who were ineligible for transplantation
- Included patients with Germinal Center B-Cell (GCB) and non-GCB subtypes

N=134

Oral Selinexor 60 mg

selinexor twice weekly
(4 week cycle)

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SADAL: A Phase 2b Study In DLBCL

Selinexor 60mg twice weekly (n=134*)

OVERALL RESPONSE RATES[1,2]

All Patients

29%

CRs 13%
PRs 16%

Genetic Subsets

34%
GCB (n=59)

21%
non-GCB (n=63)

ADDITIONAL ENDPOINTS[2]

Duration of Response

- Median DOR was **9.3** months
- Most responses at first scan (**~2** months)

Overall Survival

- All patients (n=127) = **9.1** months
- Patients with CR or PR (n=36) = **Not Yet Reached**
- Patients with stable disease (n=11) = **18.3** months
- Patients with Progressive Disease or No Response (n=80) = **4.3** months

Safety:

- Most common treatment related non-hematologic adverse events (AEs) were fatigue, nausea, decreased appetite, and diarrhea, primarily Grade 1/2, and most were manageable with dose modifications and/or supportive care
- Most common Grade 3/4 AEs were thrombocytopenia, lymphopenia, neutropenia, and anemia, and most were also manageable with dose modifications and/or supportive care

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[1]XPOVIO Prescribing Information. [2] Kalakonda N, et al. Lancet Haematology. 2020.
* 134 patients included in XPOVIO Prescribing Information and 127 patients included in Kalakonda N, et al. Lancet Haematology. 2020.

APPENDIX: COMMERCIAL INSIGHTS

Highly Experienced Team Educating the Market About XPOVIO

CUSTOMER-FACING FIELD FORCE

~70 sales representatives and nurse liaisons supporting commercial launch

- **~20** average years of pharmaceutical experience
- **~12** average years of hematology / oncology experience
- **~5** average years of MM experience

Experienced account management team responsible for payors and distribution partners

Extensive patient and HCP support program anchored by KaryForward™ platform

PRESCRIBER BASE[1]

Multiple Myeloma

- **~400** accounts generate **~50%** of all prescriptions
- **~1,300** accounts generate **~80%** of all prescriptions

DLBCL

- **~3,000** physicians treat **~80%** of U.S. DLBCL patients
- **~75%** of targeted physicians are community-based
- **>50%** overlap between Karyopharm's multiple myeloma and DLBCL targets

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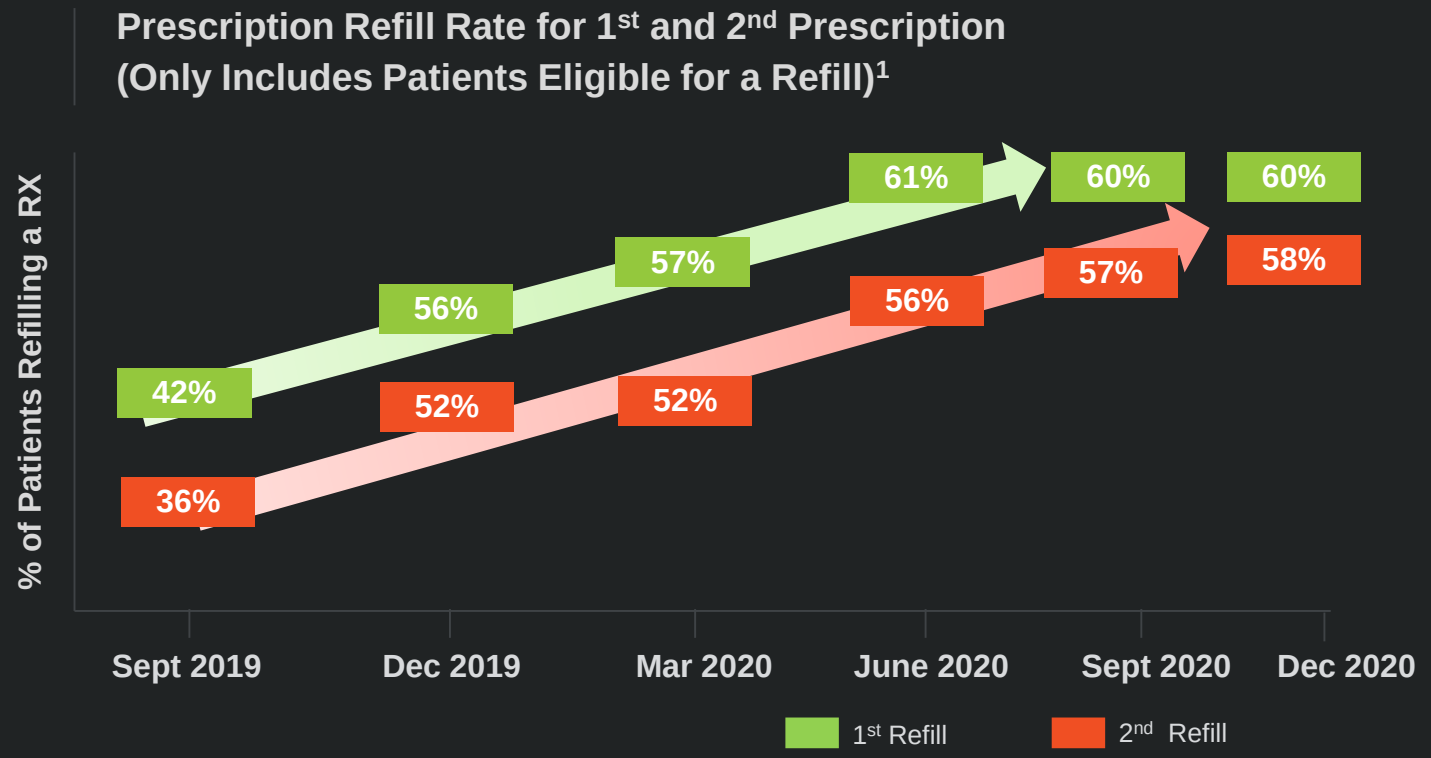
[1] Based on analysis of Symphony Claims data.

Key XPOVIO Patient Metrics in 2020



2.9[1]

Average Treatment Cycles (RXs) Per Patient

13%[1]

Patient Discontinuation Rate Due to Side Effects

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[1] Based on patient data from Karyopharm's network of specialty pharmacy providers; prescription refill rates from Sept 2019-Dec 2020, average treatment cycles per patient as of the end of Dec 2020 and discontinuation rate due to side effects at end of 2020.

Drugs with Stand-Alone (± Steroid) Anti-MM Activity and Approved for 1st or 2nd Line Treatment have Achieved >$1B in Annual Sales

2020 Worldwide Sales[1]

Immunomodulatory Agents	• **Revlimid®: $12B** • **Pomalyst®: $3B**
Proteasome Inhibitors	• **Velcade®: >$1B** • **Kyprolis®: >$1B**
Monoclonal Antibodies	• **Darzalex®: >$4B**

[1] EvaluatePharma, February 2021.

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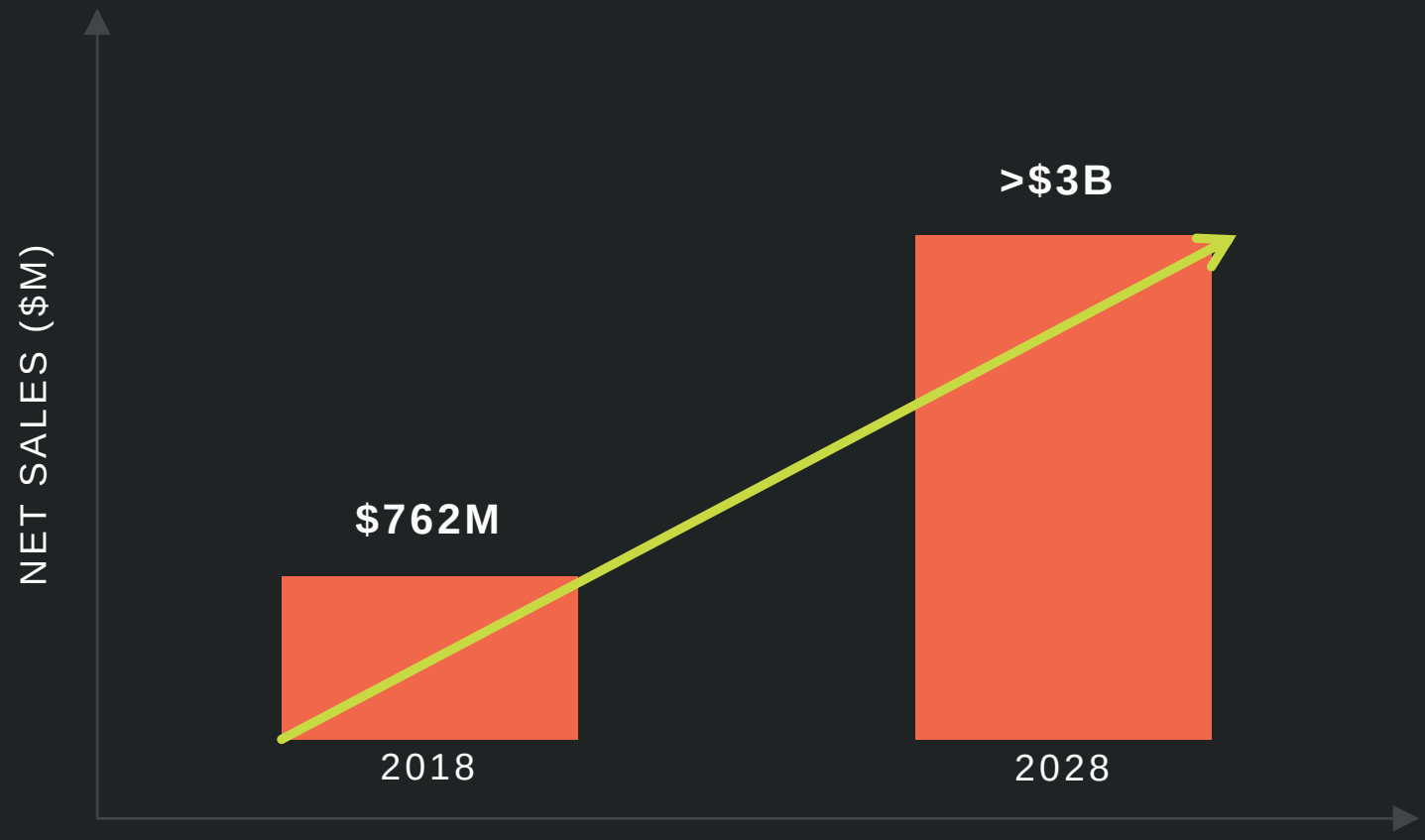
Total U.S. Drug Sales in Relapsed or Refractory DLBCL Expected to Grow from $762M in 2018 to Over $3B by 2028

Total Drug Sales in Relapsed or Refractory DLBCL[1]



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[1] Decision Resources NHL and CLL Landscape and Forecast, 2019