



Fourth Quarter and Full Year 2021 Financial Results & Business Update

February 8, 2022

Forward-looking Statements and Other Important Information

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Karyopharm's guidance on its 2022 net product revenues and 2022 non-GAAP research and development and selling, general and administrative expenses; Karyopharm's expected cash runway; the ability of selinexor or eltanexor to treat patients with multiple myeloma, diffuse large B-cell lymphoma, solid tumors and other diseases; and expectations related to future clinical development and potential regulatory submissions of selinexor and eltanexor. Such statements are subject to numerous important factors, risks and uncertainties, many of which are beyond Karyopharm's control, that may cause actual events or results to differ materially from Karyopharm's current expectations. For example, there can be no guarantee that Karyopharm will successfully commercialize XPOVIO; that regulators will grant confirmatory approval in the European Union based on the BOSTON study in adult patients with multiple myeloma; or that any of Karyopharm's drug candidates, including selinexor and eltanexor, will successfully complete necessary clinical development phases or that development of any of Karyopharm's drug candidates will continue. Further, there can be no guarantee that any positive developments in the development or commercialization of Karyopharm's drug candidate portfolio will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other factors, including the following: the risk that the COVID-19 pandemic could disrupt Karyopharm's business more severely than it currently anticipates, including by negatively impacting sales of XPOVIO, interrupting or delaying research and development efforts, impacting the ability to procure sufficient supply for the development and commercialization of selinexor or other product candidates, delaying ongoing or planned clinical trials, impeding the execution of business plans, planned regulatory milestones and timelines, or inconveniencing patients; the adoption of XPOVIO in the commercial marketplace, the timing and costs involved in commercializing XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; the ability to obtain and retain regulatory approval of XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; Karyopharm's results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. Food and Drug Administration and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, including with respect to the need for additional clinical studies; the ability of Karyopharm or its third party collaborators or successors in interest to fully perform their respective obligations under the applicable agreement and the potential future financial implications of such agreement; Karyopharm's ability to enroll patients in its clinical trials; unplanned cash requirements and expenditures; development or regulatory approval of drug candidates by Karyopharm's competitors for products or product candidates in which Karyopharm is currently commercializing or developing; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any of its products or product candidates. These and other risks are described under the caption "Risk Factors" in Karyopharm's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, which was filed with the Securities and Exchange Commission (SEC) on November 3, 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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On Today's Call

- **Welcome**

Sarah Connors, *Vice President, Corporate Communications*

- **Overview**

Richard Paulson, *President and Chief Executive Officer*

- **Commercial Highlights**

Sohanya Cheng, *Chief Commercial Officer*

- **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

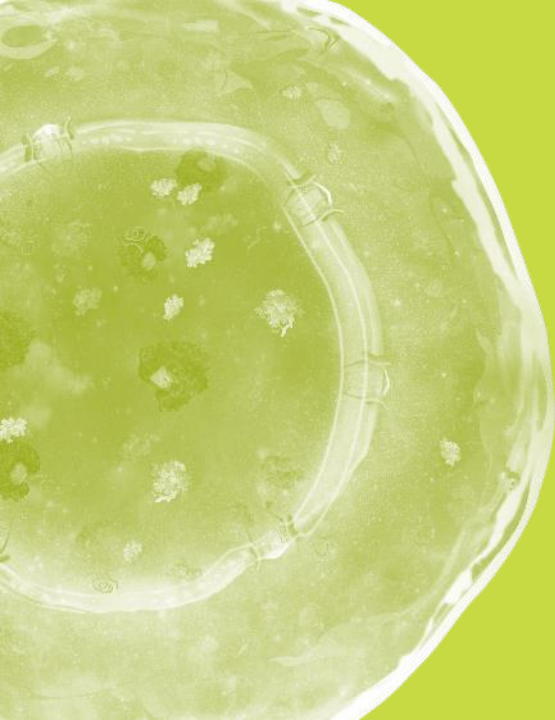
- **Sharon Shacham, PhD**

Chief Scientific Officer

Richard Paulson
Chief Executive Officer

OVERVIEW





Leveraging the
**inhibition of
nuclear export**
as a mechanism
to treat cancer



**Passionately driven in its
mission to positively impact
lives and defeat cancer**

**Expanding
on myeloma
foundation**

Expecting opinion on
MAA in 2L+
in 1H22; pursuing
additional 2L+
indications

**Near-term
opportunity in
solid tumors**

SIENDO met primary
endpoint with
statistically significant
50% improvement in
median PFS versus
placebo

**Focused clinical
pipeline**

Pursuing approvals
in MDS and myelofibrosis
over
the next 3-4 years

**Strong executive
leadership**

Ability to achieve
commercial and
development excellence to
execute corporate
objectives

Well-capitalized

Cash runway into early
2024

Prioritized and targeted core programs focused on areas of high unmet need driving continued and sustained innovation across our pipeline

MULTIPLE MYELOMA

~46,000 patients (2L+)^{1,5}

Growing adoption of approved regimens and generating data for novel combinations in 2L+

ENDOMETRIAL CANCER

~14,000 frontline patients^{2,5}

Potential to be first and only treatment post chemotherapy in the maintenance setting

MYELOFIBROSIS

~5,000 JAKi-refractory MF patients⁴

Potential to improve patient outcomes in JAKi-refractory MF

MYELOYDYSPLASTIC SYNDROMES

~15,000 intermediate to high risk patients^{3,5}

Potential to improve survival in HMA-refractory MDS

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



Sohanya Cheng
Chief Commercial Officer

COMMERCIAL HIGHLIGHTS

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

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



Once Weekly
(previously twice weekly)

Lower Dose
(previously a higher dose)

XPOVIO-based Triplets
(previously a doublet)

Earlier Lines
(previously only in later lines)

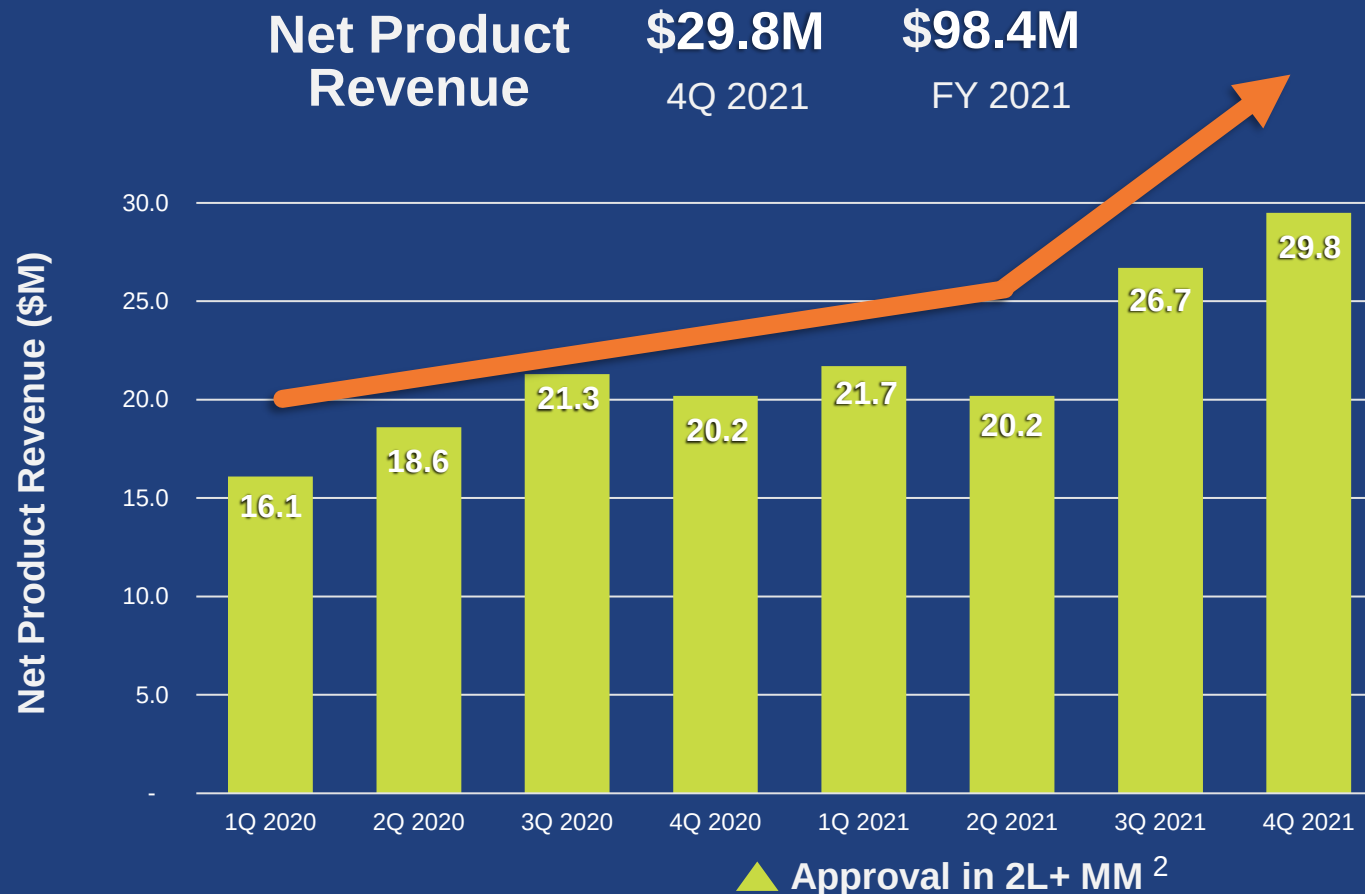
Supportive Care
(active symptom management)

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

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

XPOVIO Launch Update: 4Q/YE 2021

Sustained Growth in 2L-4L



4Q/YE 2021 Highlights

- Net product revenue up 29% for 2021 versus 2020
- Net product revenue up 47% 4Q21 versus 4Q20
- Increased uptake in 2L to 3L¹; fastest growing MM therapy used in 3L regimens¹
- Continued increase in breadth and depth of use of XPOVIO
- Building confidence in community and continued positive shift in intent-to-prescribe metrics

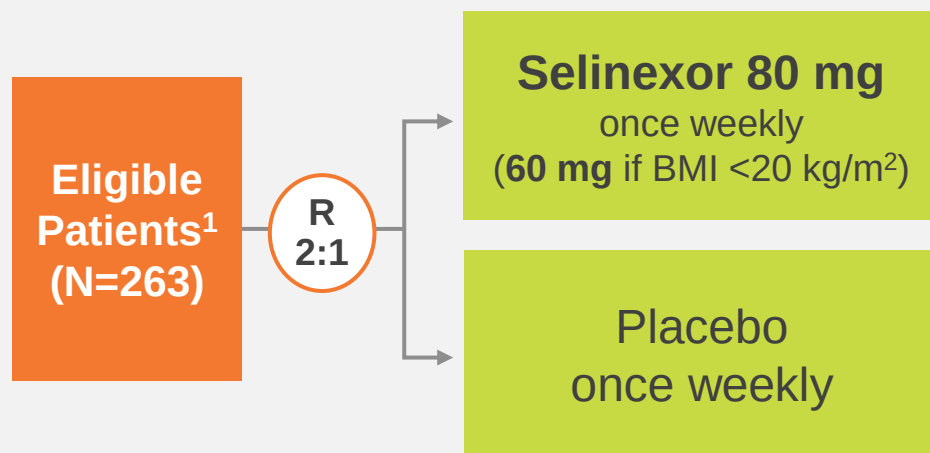


Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
Chief Commercial Officer

PHASE 3 SIENDO DATA IN ENDOMETRIAL CANCER

Phase 3 SIENDO Results Confirm Selinexor's Potential to Significantly Extend Remission in Patients with Advanced or Recurrent Endometrial Cancer



Primary Endpoint

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

Preliminary Top-line Results

- Selinexor demonstrated a statistically significant 50% increase in median PFS compared to placebo (5.7 months vs 3.8 months) (p=0.0486)
- Hazard ratio (HR) = 0.70 (CI: 0.49-0.99); representing 30% reduction in risk of disease progression or death
- 37% increase in probability of being in remission at 12 months (25.8% for placebo vs 35.3% for selinexor)
- Selinexor generally well tolerated with no new safety signals identified and low discontinuation rate of 10.5% due to adverse events
- Patients with wild-type p53 (current n=103) achieved statistically significant improvement in PFS of 13.7 months vs 3.7 months (HR: 0.38; p=0.0006)

Full Data to be Submitted for Presentation at Medical Meetings in 1H 2022

sNDA Planned to be Submitted to FDA in 1H 2022

Endometrial Cancer is the Most Common Gynecologic Cancer with Significant Unmet Need for Patients with Advanced or Recurrent Disease

What is Endometrial Cancer?

- Arises from the endometrium, the layer of cells that form the lining of the uterus.

Treatment Landscape

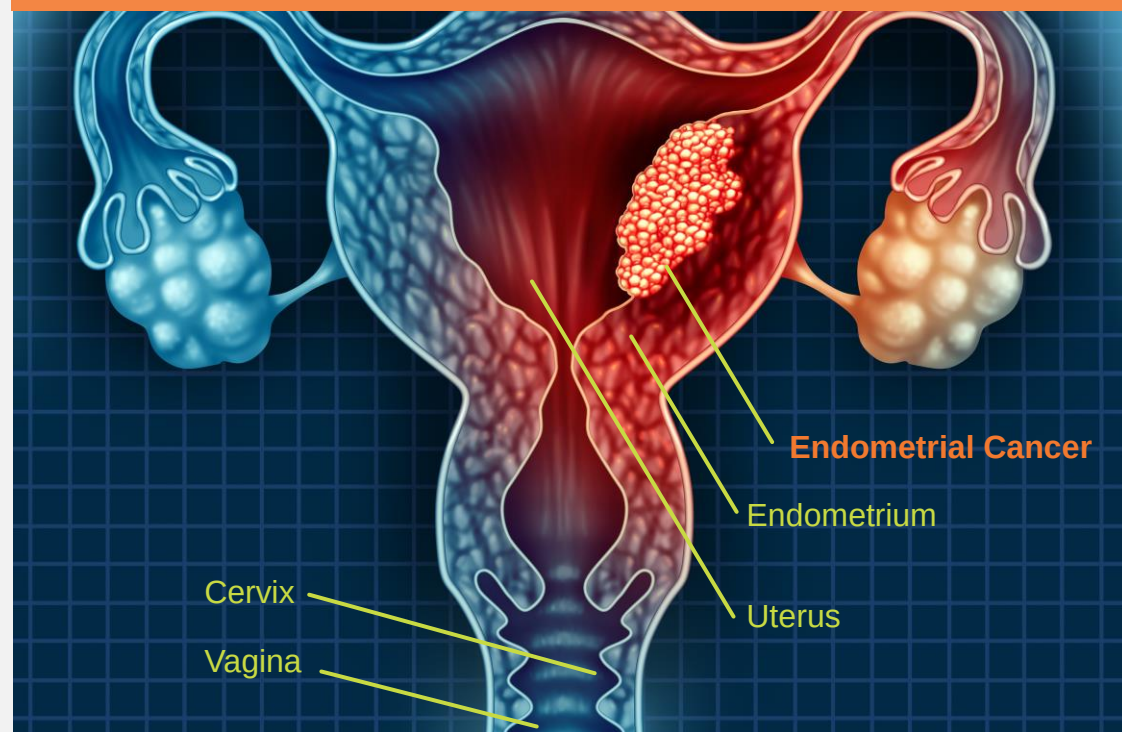
- First-line treatment is chemotherapy (taxane plus platinum), where response rates (CR or PR) can be as high as 67%³
- Following chemotherapy, NCCN Guidelines[®] recommend “watch and wait” until disease relapses⁴

Unmet Need

- Prognosis is poor, with **progression expected within ~4 months⁵** for patients responding to first-line chemotherapy treatment
- **No SoC or FDA-approved agent for maintaining response in EC** post-systemic treatment to prevent or delay progression to later lines of treatment

The safety and efficacy of selinexor in endometrial cancer has not been established and has not been approved by the US FDA or any other regulatory authority.

There will be nearly 66,000 new cases diagnosed in the U.S. in 2022¹ and more than 130,000 cases in Europe²

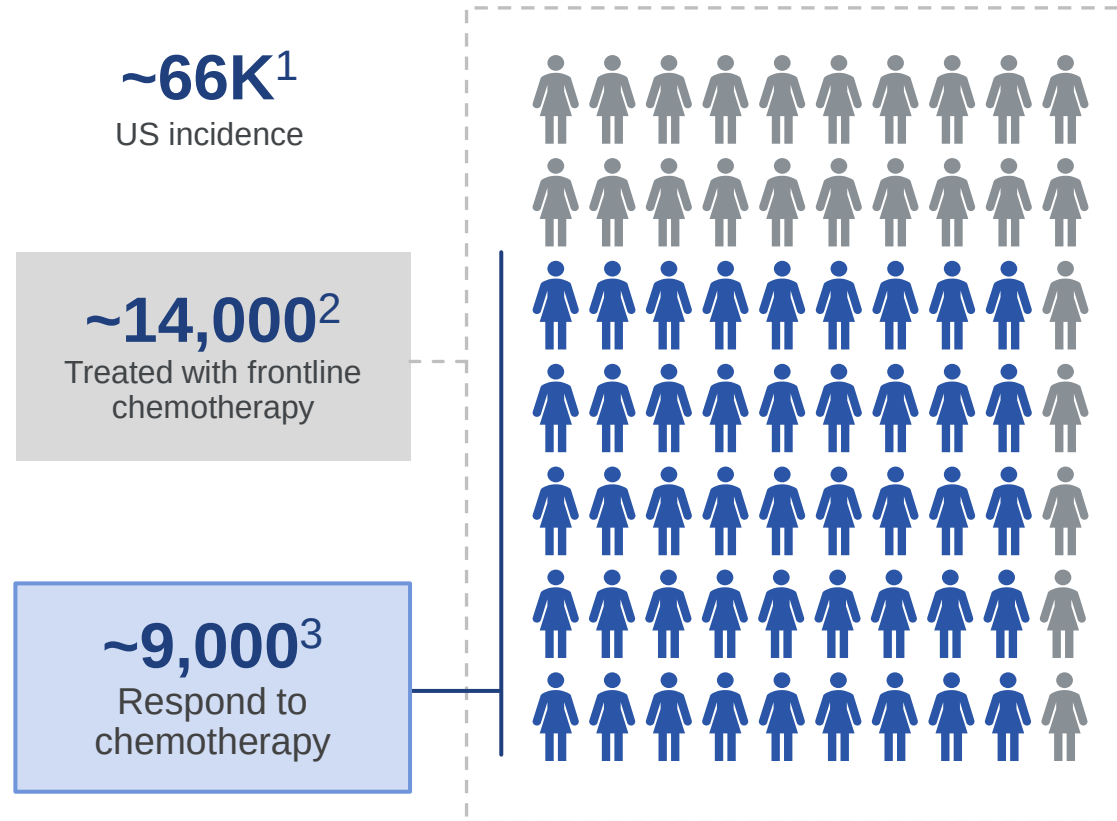


1. American Cancer Society, “About and Key Statistics.” Endometrial Cancer. <https://www.cancer.org/content/dam/CRC/PDF/Public/8609.00.pdf>

2. International Agency for Research on Cancer, World Health Organization. “Corpus uteri Fact Sheet.” Cancer Today, 2020. <https://gco.iarc.fr/today/data/factsheets/cancers/24-Corpus-uteri-fact-sheet.pdf> 3. Sorbe, B. et al. Int J Gynecol Cancer. 2008). 4. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Uterine Neoplasms. v4.2021. September 3, 2021; www.nccn.org.

5. Based on progression after 6 cycles of CP; Lorusso D. et al, 2015 by American Society of Clinical Oncology

Significant U.S. Market Opportunity for Selinexor in Endometrial Cancer based on Frontline Maintenance Potential Alone



 = 200 patients

The safety and efficacy of selinexor in endometrial cancer has not been established and has not been approved by the US FDA or any other regulatory authority.

Market Opportunity Drivers

- Maintenance therapy is **well established with physicians** in multiple solid tumors, including ovarian and breast cancer
- **PFS of 5.7 months** statistically significant compared to “watch and wait” approach (3.8 months on placebo)
- Patients **treated until progression** in the maintenance setting
- **First and only, oral treatment** post chemotherapy in the maintenance setting
- **Established and strong commercial and medical affairs footprint**, rapidly engaging in pre-launch activities

SIENDO Results Represent the Potential for a Significant Paradigm Shift for the Treatment of Women with Advanced or Recurrent Endometrial Cancer

Phase 3 SIENDO study met primary endpoint

Selinexor
improved PFS
by 50%
with a HR=0.70
(p=0.0486)

Addressing a significant unmet need

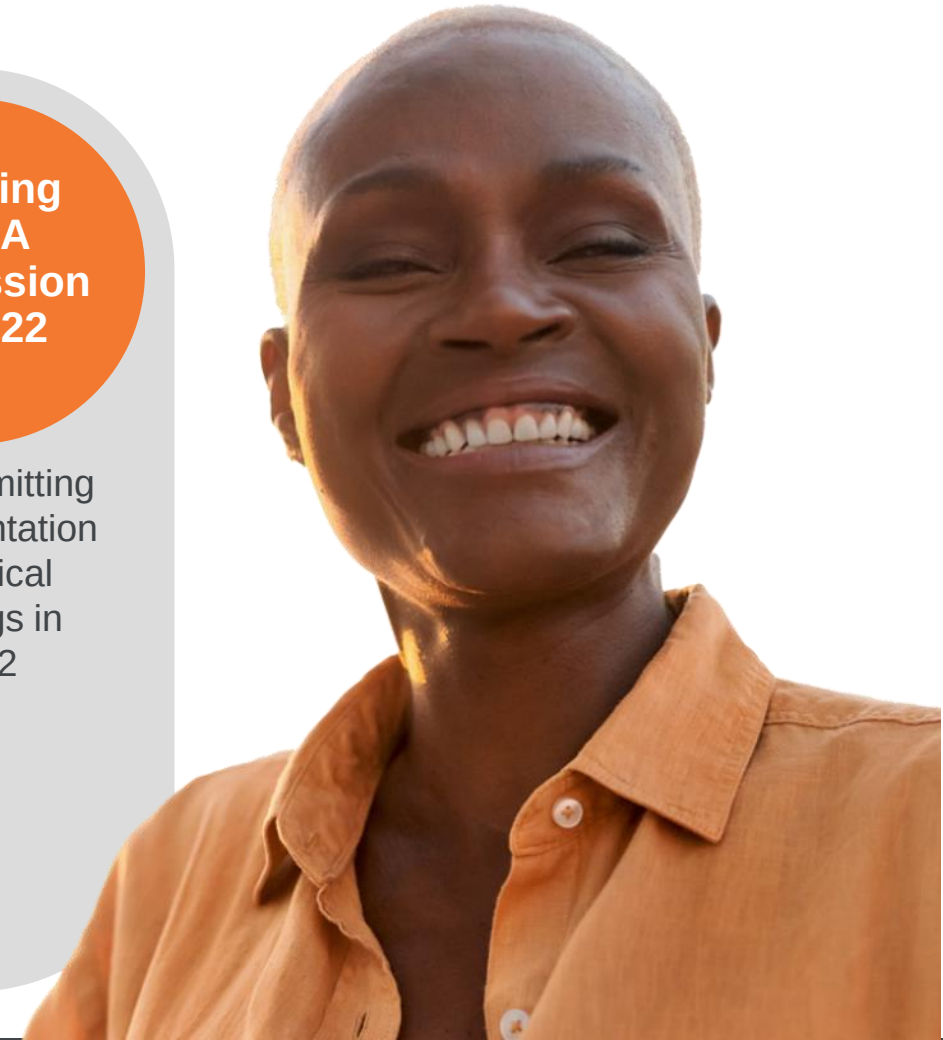
Currently
no FDA approved
treatments in the
maintenance
setting

Significant market opportunity

Based on
14,000 patients
treated with
frontline
chemotherapy

Planning sNDA submission in 1H22

Also submitting
for presentation
at medical
meetings in
1H22

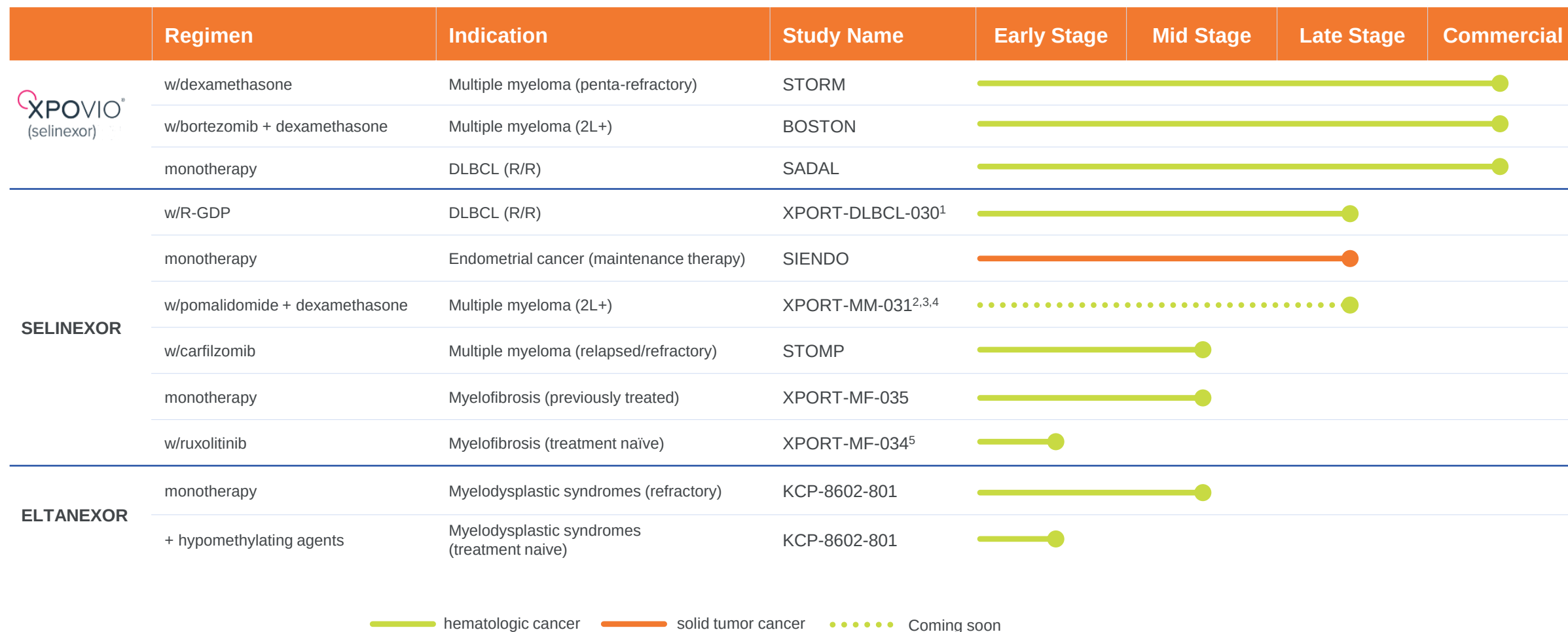




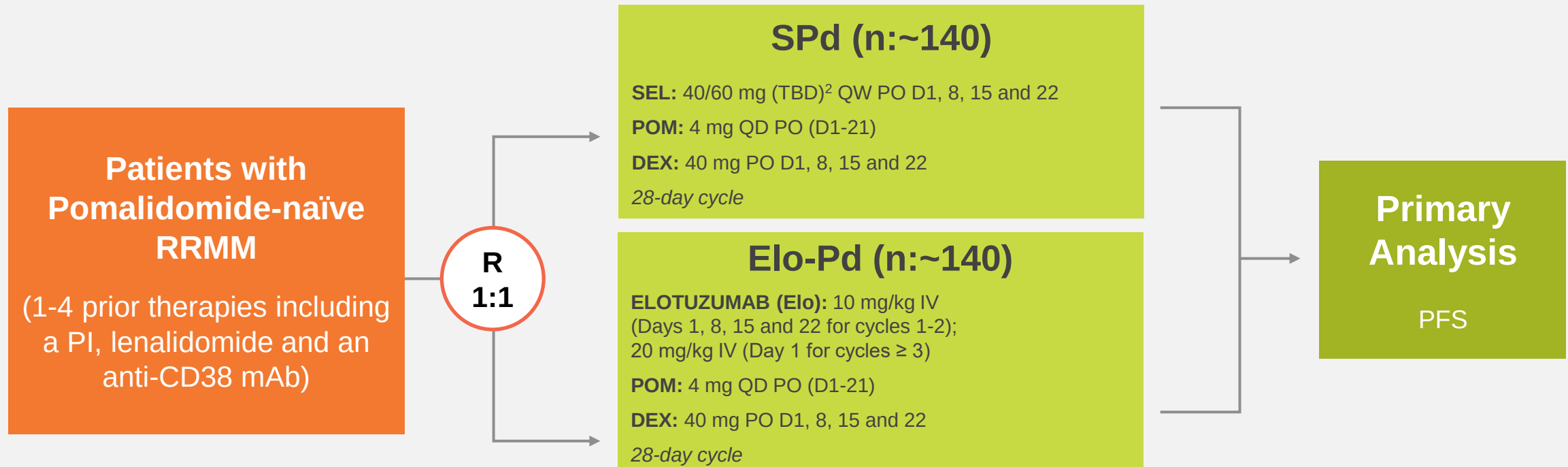
Jatin Shah, MD
Chief Medical Officer

OTHER CORE PROGRAMS

Progressing Focused Pipeline Across Cancers With High Unmet Needs



Phase 3 Study Evaluating Selinexor, Pomalidomide and Dexamethasone (SPd) in Patients with Previously Treated Multiple Myeloma¹



Expect to dose first patient in 1Q 2022
Top-line data expected 2024

Ongoing Progress With Global Selinexor Access

Europe

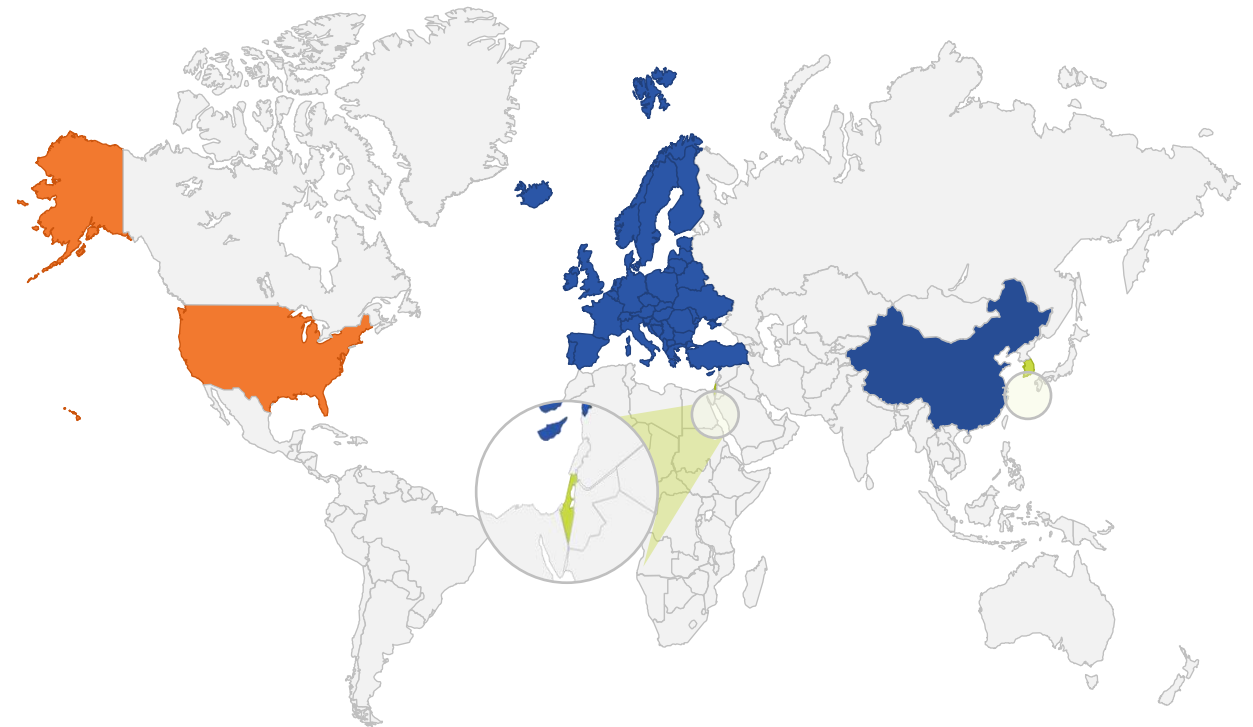
- MAA validated and under review by CHMP for 2L+; expect review to be completed in 1H22

Asia

- Antengene received conditional approval in China for penta-refractory multiple myeloma
- NDAs submitted by Antengene in multiple additional Asia Pacific markets including Hong Kong, Australia, Singapore and Taiwan¹

Canada

- NDS in 2L+ filed by Forus Therapeutics and accepted for review by Health Canada



- 2L+ multiple myeloma and R/R DLBCL
- Penta-refractory multiple myeloma
- Penta-refractory multiple myeloma and R/R DLBCL²

MYELOFIBROSIS



Selinexor Has the Potential to Improve Patient Outcomes in JAKi Refractory Myelofibrosis

What is Myelofibrosis (MF)?

- Type of bone marrow cancer that disrupts body's normal production of blood cells.
- Causes extensive scarring in bone marrow, leading to severe anemia that can cause weakness and fatigue

Treatment Landscape

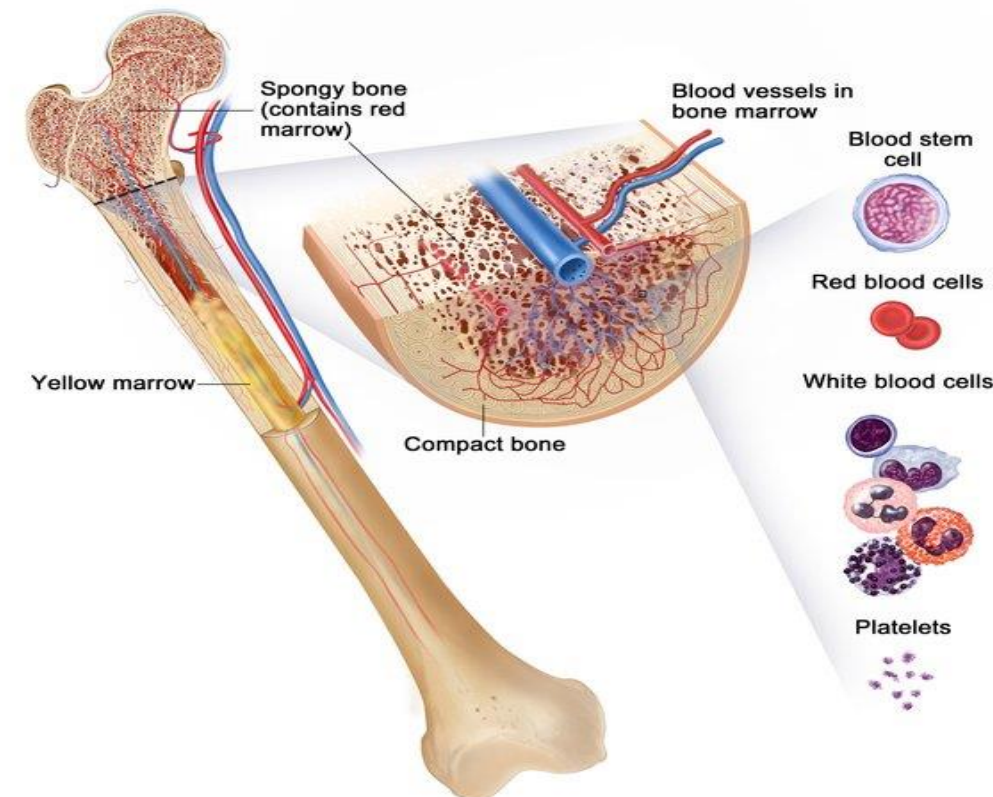
- Ruxolitinib is the standard of care for patients with newly diagnosed MF and it has resulted in splenic and clinical responses up to 4 years for primary responders
- Approximately 40% of patients respond²

Opportunity and Unmet Need

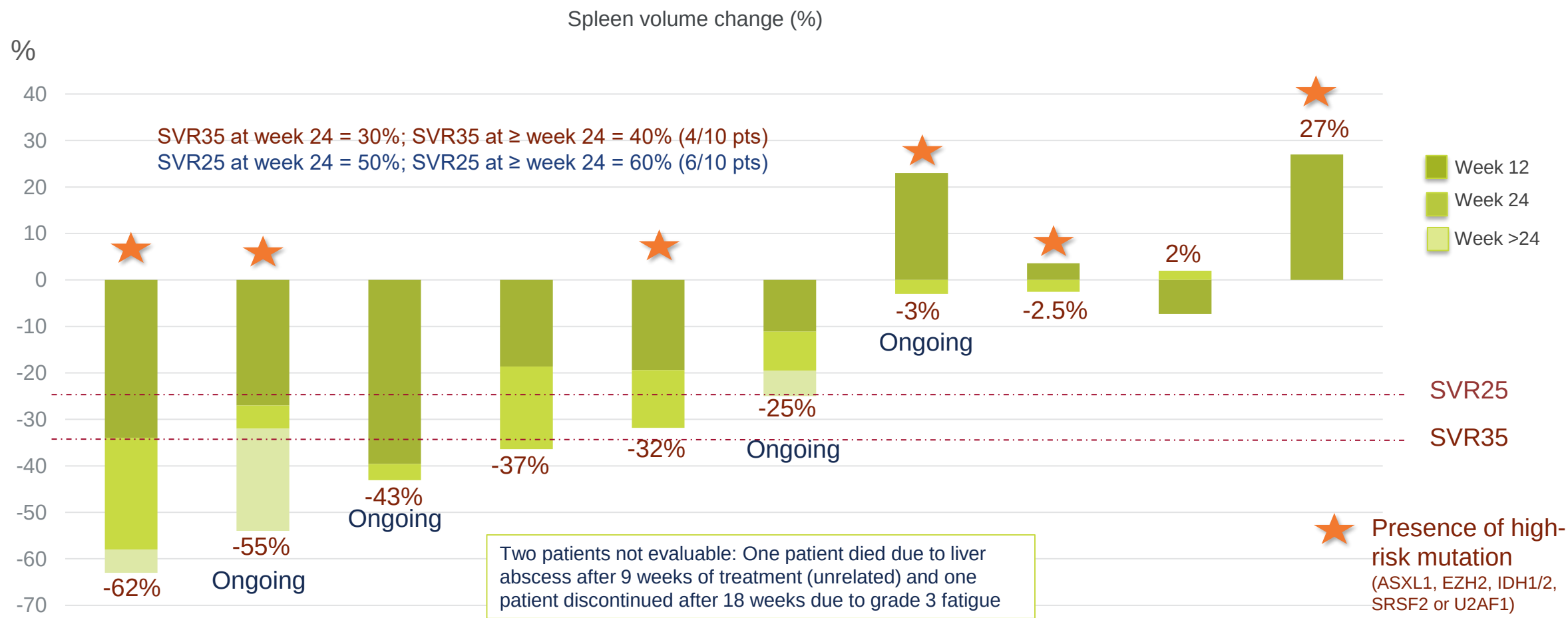
- Prognosis in ruxolitinib-refractory disease is poor, with an **expected median survival of ~14 months**³
- No other class of therapies other than JAK inhibitors

The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the US FDA or any other regulatory authority.

It is estimated that ~5,000 cases of MF occur in the US annually¹

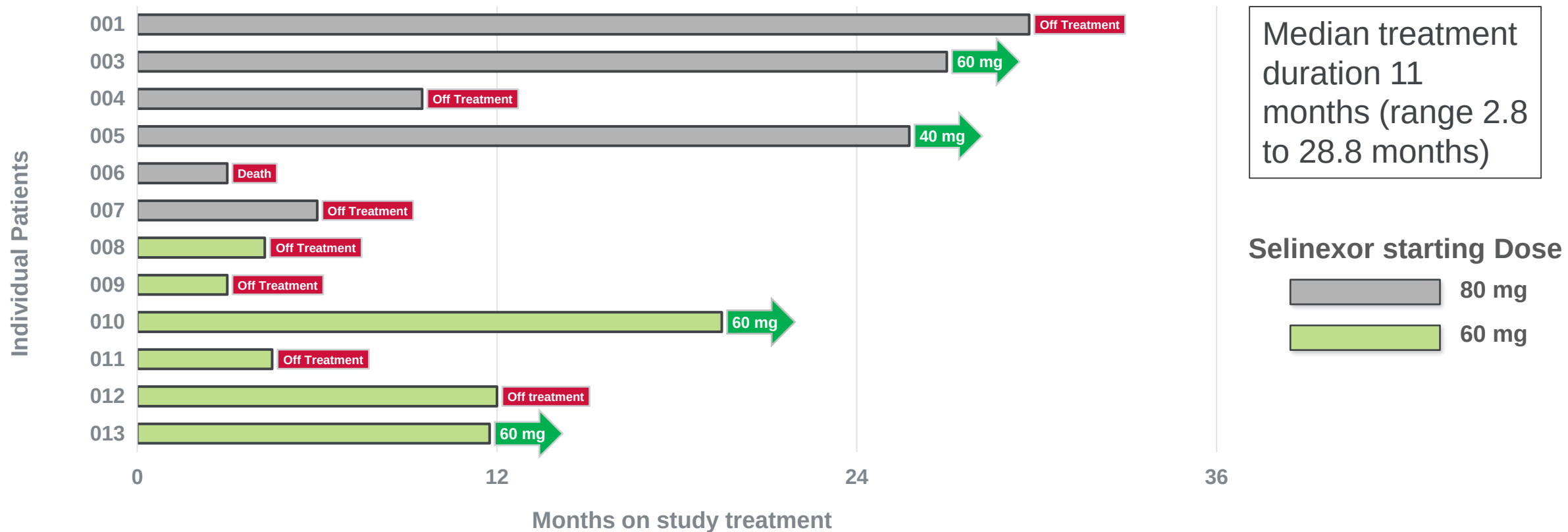


Single-Agent Selinexor Resulted in Sustained Spleen Responses in Refractory MF Patients¹



The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the US FDA or any other regulatory authority.

Single-Agent Selinexor Resulted in Durable Responses with Long Term Therapy Documented Beyond Two Years¹

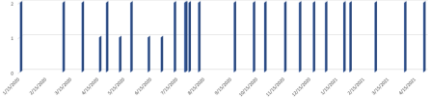


Eight pts (70%) discontinued Selinexor due to: progression (n=2; 1 spleen size progression and 1 AML), changed to another clinical trial (n=2), death (n=1), and toxicity (n=3; 1 fatigue and 2 weight loss)

The safety and efficacy of selinexor in myelofibrosis not been established and has not been approved by the US FDA or any other regulatory authority.

1. Tantravahi, et al. ASH 2021.

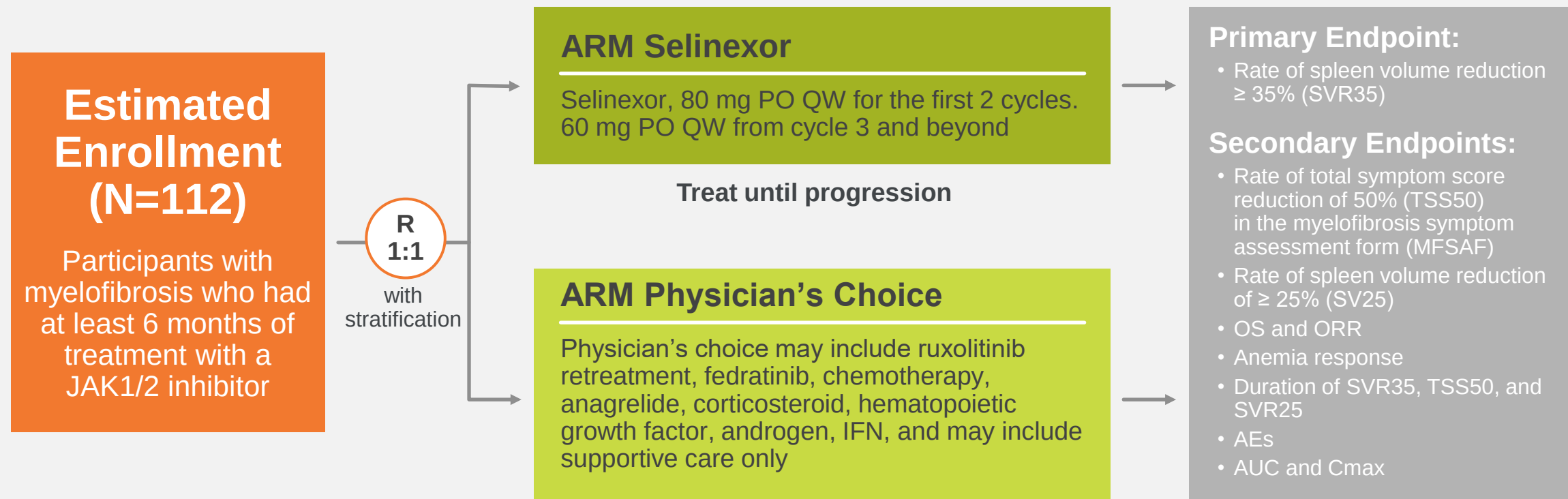
Among Patients with Anemia or Transfusion Dependence 50% Achieved Improved Hemoglobin Levels or Transfusion Independence

Patient	Baseline	Best response	Transfusion requirements
01-001	TD	Became TI	
01-003	TD ($<6\text{u}/12\text{ weeks}$)	Became TI	
01-004	TD	Unchanged	
01-010	TD	Unchanged	
01-011	TD	Unchanged	(chart not available)

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

Patient	At screening	Best response	Anemia response
01-005	Hgb 8.7	Hgb 13.7	2.0 g/dl increase
01-008	Hgb 9.3	Hgb 10.5	1.2 g/dl increase
01-012	Hgb 9.7	Hgb 11.8	2.1 g/dl increase

A Company-sponsored Phase 2 Study Evaluating Single-Agent Selinexor Versus Physician's Choice in Previously Treated MF



First patient dosed December 2021
Top-line data expected 2H 2023

MYELODYSPLASTIC SYNDROMES



Eltanexor Has the Potential to Improve Survival in HMA Refractory Myelodysplastic Syndromes

What is Myelodysplastic Syndrome (MDS)?

- Blood-forming cells in marrow become abnormal and create immature blood cells that are not able to function properly

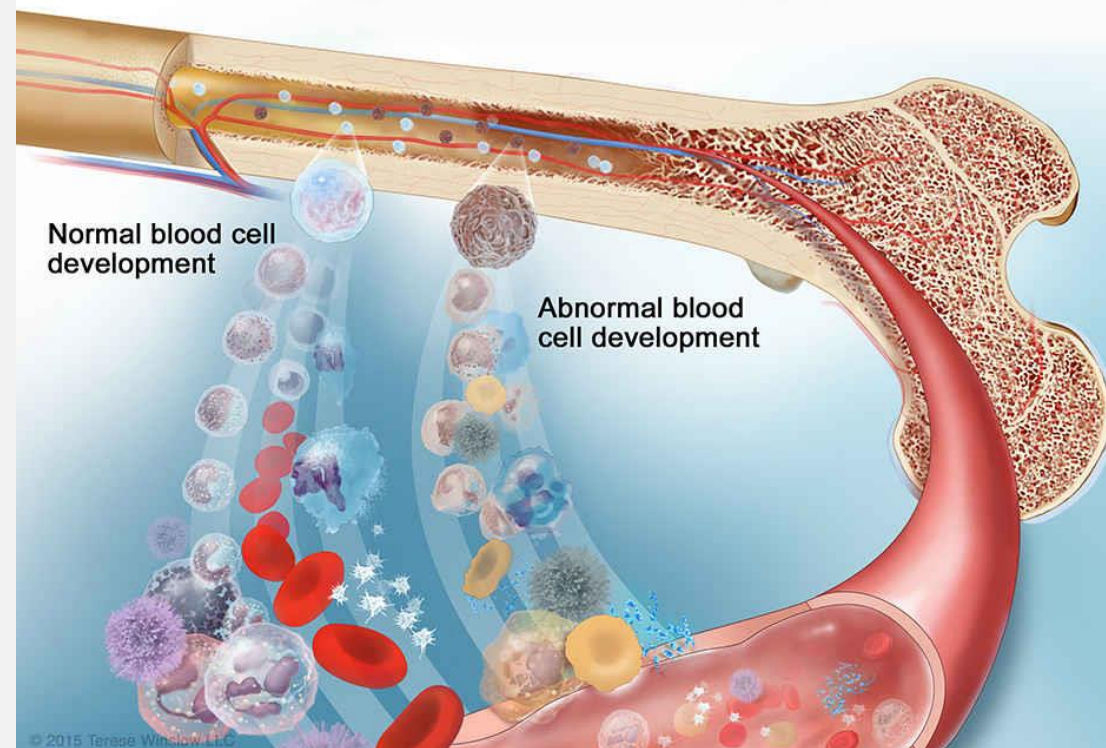
Treatment Landscape

- Hypomethylating agents (HMA) are the current standard of care for patients with newly diagnosed, higher-risk MDS
- Approximately 50% of patients respond; responses typically last <2 years²

Opportunity and Unmet Need

- Prognosis in HMA-refractory disease is poor, with an **expected survival of 4-6 months**^{3,4}
- No currently approved therapies for HMA-refractory disease

~15,000 patients diagnosed with intermediate-to-high risk MDS each year in the US¹



Single-agent Eltanexor Demonstrated Robust Activity with an ORR of 53% Among Patients With HMA Refractory MDS in a Phase 1 Study¹

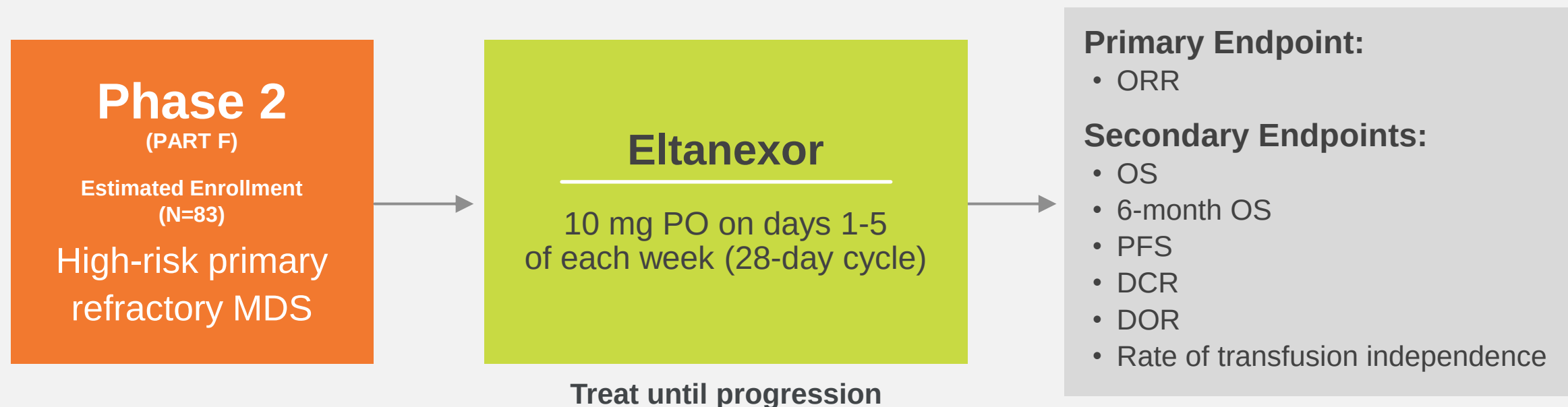
- No approved drugs and historical overall survival (OS) of 4-6 months in patients with HMA-refractory MDS
- **Single-agent eltanexor demonstrated median OS of 9.9 months**
 - Response rate correlated to OS; Median OS mCR vs PD: 11.86 vs 3.15 months (HR=0.23, p=0.04)
- **Single-agent eltanexor demonstrated 53% ORR**

	Total N=15
Overall Response Rate (mCR + HI) ^{2,3}	53%
Median treatment duration (weeks, all patients)	13.0
Median time to response (weeks)	8.4
Median duration of response (weeks)	19.2

The Grade 3/4 AEs across all patients were anemia (40%), leukopenia (20%), thrombocytopenia without bleeding (20%), decreased appetite/weight (20%), neutropenia (40%); no febrile neutropenia, 1 case of sepsis.
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.
No severe bleeding events — which is the corresponding clinical outcome for thrombocytopenia (as you have febrile neutropenia and sepsis as the clinical outcome for neutropenia).

1. Lee, Sangmin, et al. ASH 2021. 2. mCR = complete response without marrow recovery. 3. HI = hematologic improvement.

Phase 2 Expansion of the Ongoing Phase 1/2 Study of Single-Agent Eltanexor in HMA Refractory MDS



First patient dosed Sept 2021
Top-line data expected 1H 2023



MICHAEL MASON
Chief Financial Officer

FINANCIAL RESULTS AND GUIDANCE

Strategic Partnerships Driving Expansion of Our Global Footprint

Commercial Partnerships Serving Key Global Markets

NEXPOVIO® (selinexor) NOW PARTNERED
in Europe, Asia Pacific, and other key global territories

The **MENARINI** Group

Exclusively licensed rights to NEXPOVIO in European Union, the UK, Switzerland, CIS Countries and Latin America

- Karyopharm received upfront payment of \$75M in 4Q21
- Eligible to receive up to an additional \$202.5M in future milestones (based on regulatory and sales performance), plus tiered double-digit royalties on net sales ranging from the mid-teens to the mid-twenties
- Menarini to co-fund 25%, up to a maximum of \$15M per calendar year, of Karyopharm's global R&D expenses each year from 2022 to 2025

ANTENGENE

- Karyopharm recorded \$19.5 million in milestone revenue from Antengene in 4Q21



AsiaPac



EU & LatAm



Israel



Canada

4Q and FY 2021 Financial Results

Statements of Operations (\$ millions)	4Q 2021	4Q 2020	FY 2021	FY 2020
Total Revenue	\$126.3	\$35.1	\$209.8	\$108.1
XPOVIO Net Sales	29.8	20.2	98.4	76.2
License and Other Revenue	96.5	14.9	111.4	31.9
Total Operating Expenses	\$79.3	\$72.2	\$308.1	\$279.9
Cost of Sales	0.7	1.1	3.4	2.7
Research and Development Expenses	44.0	37.2	160.8	150.8
Selling, General & Administrative Expenses	34.6	33.9	143.8	126.4
Net Income (Loss)	\$38.7	(\$43.4)	(\$124.1)	(\$196.3)
Net Income (Loss) per share	\$0.46	(\$0.59)	(\$1.65)	(\$2.72)

Balance Sheet (\$MM)	Dec 31, 2021	Dec 31, 2020
Cash, Cash Equivalents, Restricted Cash and Investments	\$235.6	\$276.7

2022 Financial Guidance

- Net Product Revenue of \$135-\$145 million, reflecting ~40% growth over 2021
- Non-GAAP R&D and SG&A Expenses of \$265-\$280 million¹
- Cash runway expected to be sufficient to fund planned operations into early 2024

Richard Paulson
Chief Executive Officer

CLOSING REMARKS



Upcoming Milestones for 2022 and 2023

MULTIPLE MYELOMA

- Leverage commercial capabilities and increase US XPOVIO sales (2022)
- Dose first patient in Phase 3 study evaluating selinexor + pomalidomide + dex (Q1 2022)
- EMA decision on MAA in 2L+ based on BOSTON study¹ (1H 2022)

ENDOMETRIAL CANCER

- Submit full Phase 3 selinexor SIENDO data for presentation at upcoming medical meeting (1H 2022)
- Submit sNDA (1H 2022)
- Conduct pre-launch activities (2022)
- Potential approval and launch as a maintenance therapy (1H 2023)

MYELOFIBROSIS

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

MYELODYSPLASTIC SYNDROMES

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

Q&A SESSION

