Karyopharm® Therapeutics

Business Highlights & Third Quarter 2021 Financial Results

November 3, 2021

On Today's Call

- **Welcome**
  Jason Finkelstein, *Investor Relations, Argot Partners*
- **Overview**
  Richard Paulson, *President and Chief Executive Officer*
- **Commercial Highlights**
  Sohanya Cheng, *SVP, Sales and Commercial Operations*
- **Clinical Pipeline Updates**
  Jatin Shah, MD, *Chief Medical Officer*
- **Financial Summary and Guidance**
  Michael Mason, *Chief Financial Officer*
- **Closing Remarks**
  Richard Paulson, *President and Chief Executive Officer*
- **Q&A Session**

Joining for Q&A:

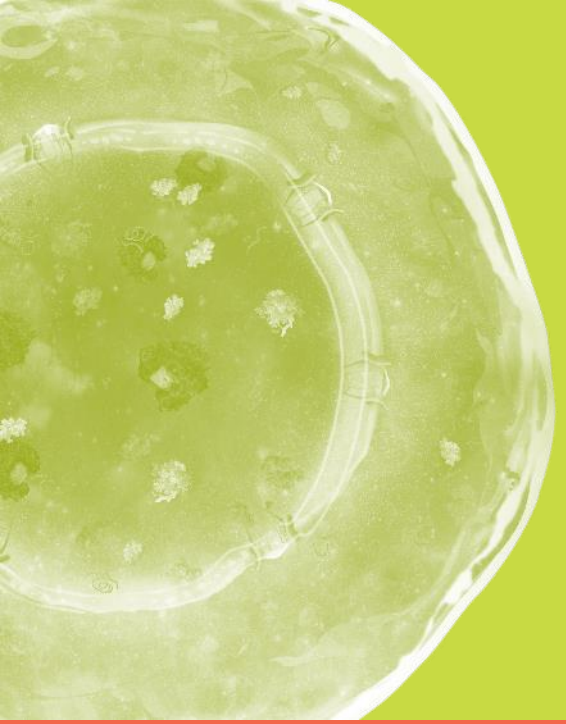
- **Stephen Mitchener, PharmD**
  Chief Business Officer
- **Sharon Shacham, PhD**
  Chief Scientific Officer

Forward-looking Statements and Other Important Information

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Karyopharm's guidance on Karyopharm's 2021 non-GAAP research and development and selling, general and administrative expenses; Karyopharm's expected cash runway; expectations and plans relating to XPOVIO for the treatment of adult patients with relapsed or refractory multiple myeloma or relapsed or refractory diffuse large B-cell lymphoma and other hematologic malignancies and solid tumors; commercialization of XPOVIO or any of Karyopharm's drug candidates and the commercial performance of XPOVIO; submissions to, and the review and potential approval of selinexor or eltanexor 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 or 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 or 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 June 30, 2021, which was filed with the Securities and Exchange Commission (SEC) on August 5, 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.

Richard Paulson
Chief Executive Officer

OVERVIEW



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

XPOVIO® (selinexor) 20 mg tablet

APPROVED IN THE US FOR 3 INDICATIONS[1]

- Multiple myeloma as early as first relapse[2]
- Relapsed/refractory diffuse large B-cell lymphoma[3,4]

Building on myeloma foundation

Driving depth and breadth of leadership presence in myeloma

Expanding global footprint

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

SIENDO recruitment on track

Top-line results in endometrial cancer by year end / early 2022

Focused clinical pipeline

Targeting high unmet need in hematological and solid tumor cancers

Well-capitalized

Cash runway into mid-2023

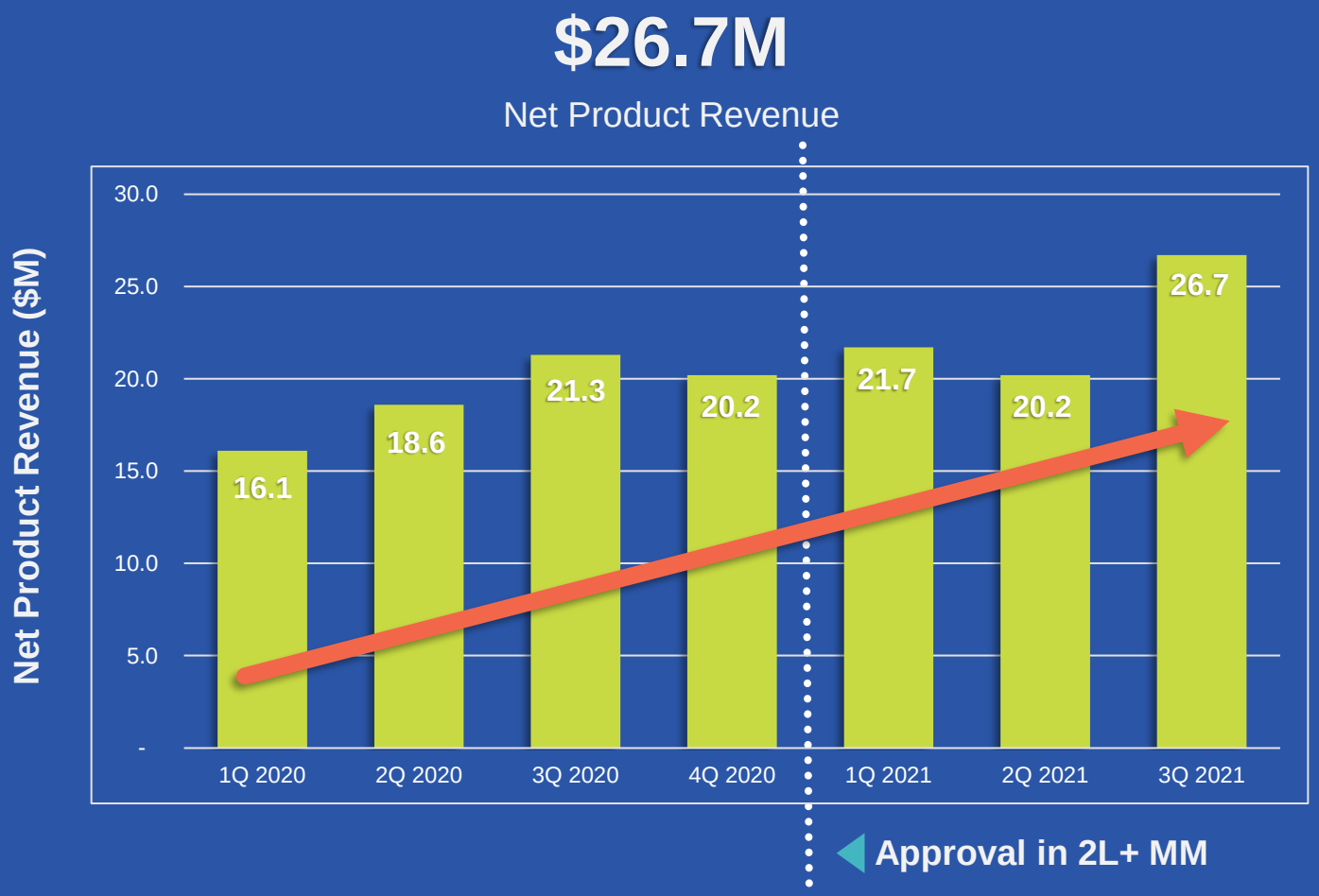
1. Approved only in combination with Velcade® and dexamethasone for patients who have received at least one prior therapy. Full Prescribing Information available at XPOVIO.com 2. XPOVIO is approved in the US and Europe for the treatment of penta-refractory multiple myeloma, and in the US for second-line and higher multiple myeloma. 3. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. 4. 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).

Sohanya Cheng
Head of Sales &
Commercial Operations

COMMERCIAL HIGHLIGHTS

XPOVIO Launch Update: 3Q 2021

Accelerated Growth in 2L+



3Q 2021 Highlights

- Net product revenue up 32% quarter-over-quarter and 25% year-over-year
- Strong demand growth representing 26% quarter-over-quarter
- RXs evolving from penta-refractory to earlier lines[1], in line with positioning and messaging
- Continue to see certain COVID impacts, but patient visits and field activities returning gradually to pre-COVID levels

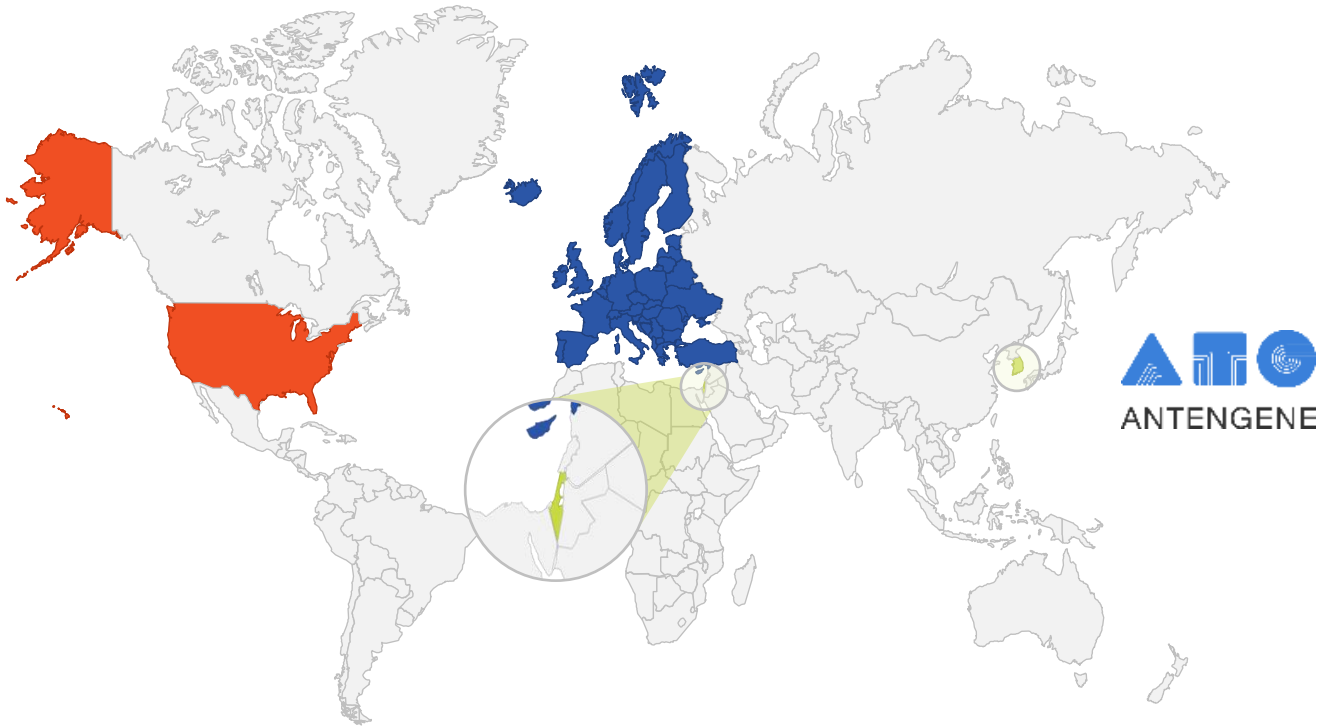
1. Komodo Health Claims Data Jan-Aug 2021 and BrandImpact Treatment Audit Jan-July 2021.

Jatin Shah, MD
Chief Medical Officer

CLINICAL PIPELINE UPDATES

Ongoing Progress With Global Selinexor Access

- Marketing Authorization Application validated and under review by CHMP (based on Phase 3 BOSTON clinical data); Expect review to be completed in 1H22
- New Drug Submission (based on Phase 3 BOSTON clinical data) filed by partner Forus Therapeutics and accepted for review by Health Canada
- New Drug Applications submitted by partner Antengene in multiple Asia Pacific markets including China, Hong Kong, Australia, Singapore and Taiwan[1]



2L+ multiple myeloma and R/R DLBCL

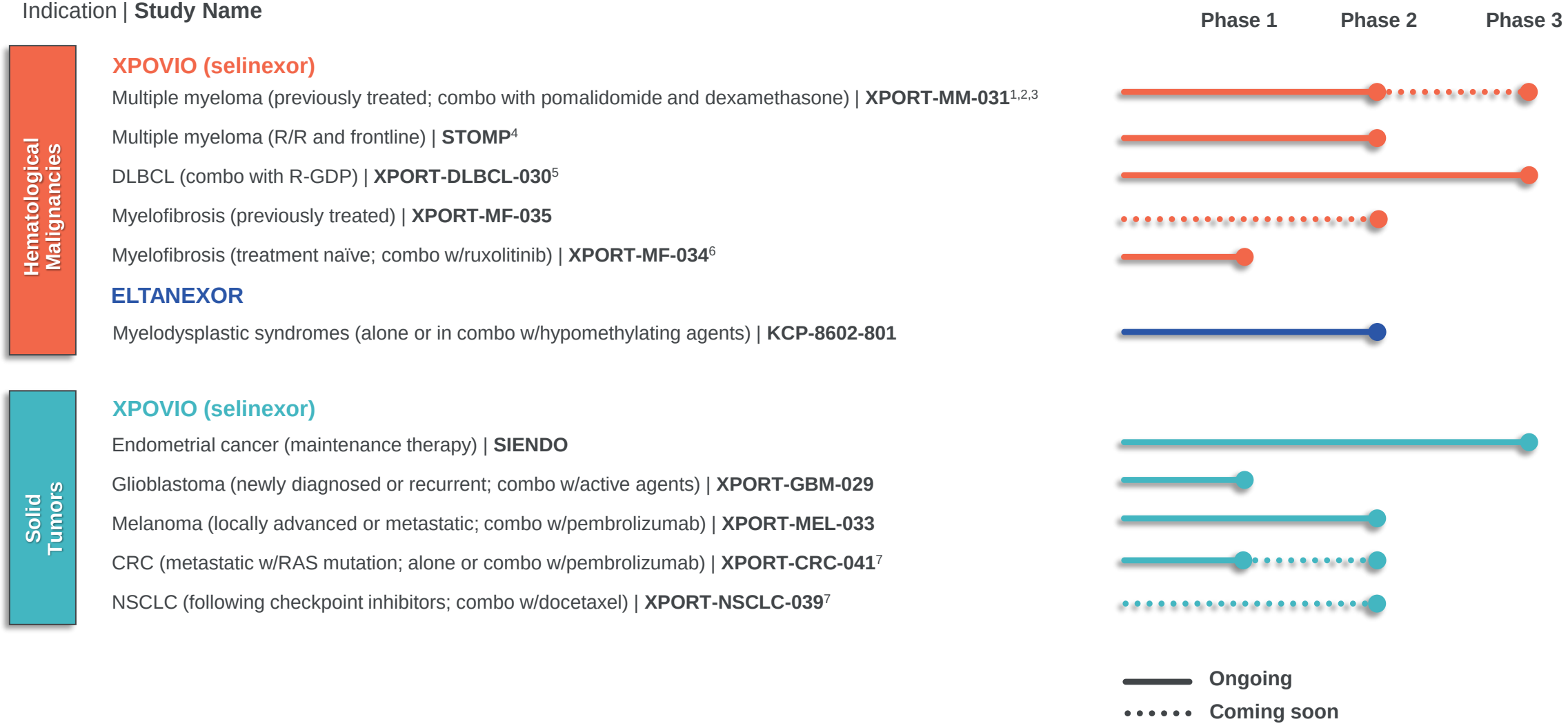
Penta-refractory multiple myeloma

Penta-refractory multiple myeloma and R/R DLBCL[2]

1. Antengene press release dated June 4, 2021. 2. Approved in Israel and South Korea.

Progressing Pipeline Across Multiple Cancers With High Unmet Needs

Indication | **Study Name**



1. Versus elotuzumab, pomalidomide, and dexamethasone. 2. Study expected to start in 2021. 3. Sponsored by European Myeloma Network. 4. Oral selinexor and dexamethasone + bortezomib, carfilzomib, daratumumab, elotuzumab, ixazomib, lenalidomide, pomalidomide, or belantamab mafodotin. 5. XPORT-DLBCL-030 is a Phase 2/3. 6. XPORT-MF-034 is a Phase 1/2. 7. XPORT-CRC-041 and XPORT-NSCLC-039 are supported by Phase 1 data from XPORT-STP-027.

Selinexor Has the Potential to Extend Remission in Patients with Advanced or Metastatic Endometrial Cancer

What is Endometrial Cancer?

- The **most common gynecological cancer in the US**.
- 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%[1]
- Following chemotherapy, NCCN Guidelines® recommend “watch and wait” until disease relapses[2]
- **No approved drug therapies** for post chemotherapy in the maintenance setting to prolong remission

Opportunity and Unmet Need

- Prognosis is poor, with **progression expected within 4-6** months following first-line chemotherapy treatment
- Selinexor as a maintenance therapy has the potential to prolong remission and give patients more time until relapse
- Over **66,000 women** will be diagnosed in the US in 2021[5], with **~14,000 progressing to advanced disease**[3]

Opportunity For Maintenance Therapy Post Front-line Chemotherapy

An estimated ~14,000 new cases of advanced or metastatic endometrial cancer occur in the US annually.[3]

Incidence is on the rise due to obesity, metabolic syndrome, nulliparity, and increased use of unopposed estrogens[4]

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

1. Sorbe, B et al. Int J Gynecol Cancer. 2008). 2. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Uterine Neoplasms. v4.2021. September 3, 2021; www.nccn.org. 3. EpicOncologyTM Epidemeology Database, 2020. 4 Colombo et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer. Ann Oncol. 2016; 27: 16-41. 5. SEER / NCI Cancer Stat Facts. 2021.

Selinexor Demonstrated Durable Single Agent Activity in Patients With *Progressive Disease* in Refractory Endometrial Cancer (SIGN Study)[1]

Baseline Patient Characteristics (n=23)[2,3]	
Previous lines of therapy (median, range)	2 (1-5)
Previous platinum agent	96%
Previous taxane	100%
Endpoints	
Primary Endpoint: Disease Control Rate (DCR; defined as CR/PR/SD ≥12 weeks)	35%
Secondary Endpoint: **Median Duration of DC**	**6.3 months**

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

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

1. Vergote I, et al. Gynecologic Oncology. 2019. 2. A total of 114 patients were enrolled in the SIGN study with endometrial, ovarian and cervical cancers. 3. Patients in the endometrial cancer arm received selinexor at 50 mg/m^2 twice a week.

SIENDO Study Design:

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

Eligibility

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

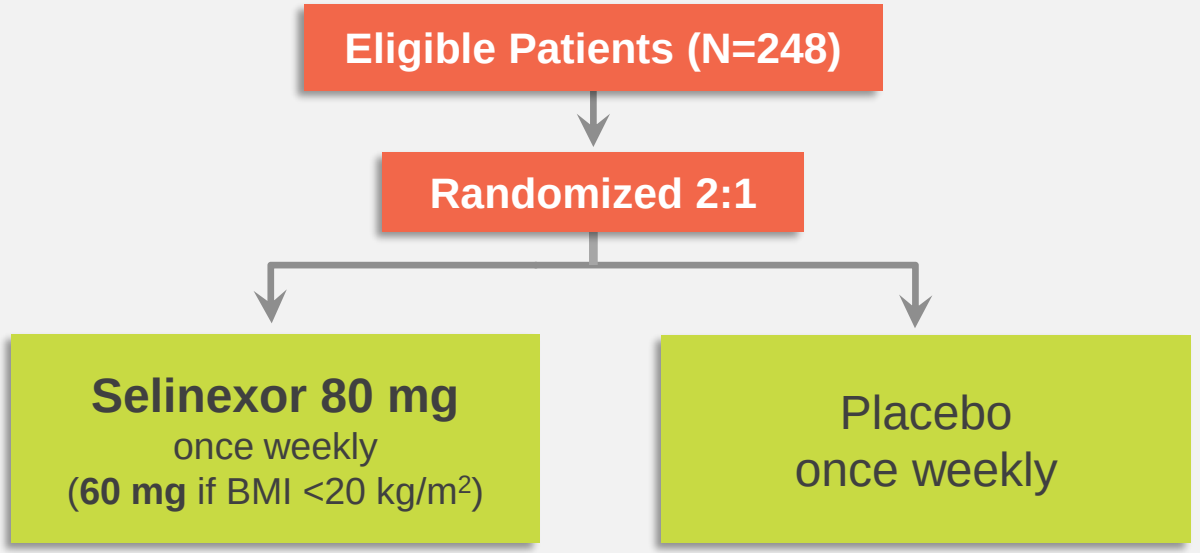
- Primary Stage IV disease
- First Relapse (i.e., relapse after primary therapy including surgery and/or adjuvant therapy for Stage I-IV disease)

Primary Endpoint

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

Statistical Design

- Hazard Ratio of 0.60 corresponds to a 67% increase in median PFS, assuming a median PFS of 4.5 months for placebo and 7.5 months for selinexor



- **Trial passed interim futility analysis in November 2020**
- **Top-line, event driven, data expected by year end / early 2022**
- **Recruitment remains on track**

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

What is MDS?

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

Treatment Landscape

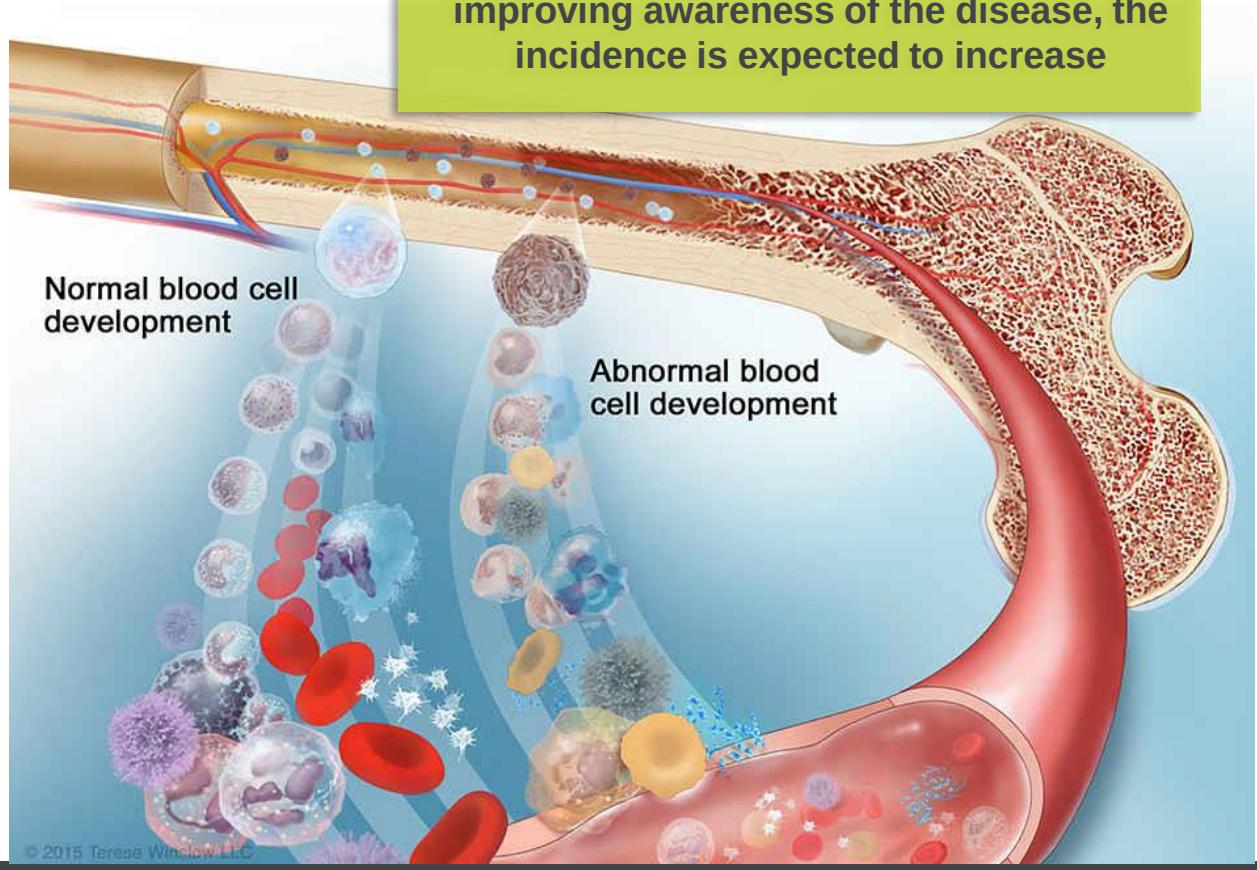
- Hypomethylating agents (HMA) are the current standard of care for patients with newly diagnosed, higher-risk MDS
- Approximately 50% of patients respond; responses typically last <2 years[2]
- **No agents approved for primary HMA-refractory MDS**

Opportunity and Unmet Need

- Prognosis in HMA-refractory disease is poor, with an **expected survival of 4-6 months**[3]
- Ongoing agents in development externally are focused in newly diagnosed MDS
- Prevalence of **60,000 in the US**

It is estimated that ~15,000 new cases of MDS occur in the US annually[1]

With an aging population and an improving awareness of the disease, the incidence is expected to increase



1. Clarivate/DRG Myelodysplastic Syndromes Landscape & Forecast (Nov 2020). 2. Gil-Perez A, et al. Management of myelodysplastic syndromes after failure of response to hypomethylating agents. Ther Adv Hematol. 2019;10:2040620719847059. Published 2019 May 9. doi:10.1177/2040620719847059.. 3. Jabbour E, et al. Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. Cancer. 2010 Aug 15;116(16):3830-4. doi: 10.1002/cncr.25247. PMID: 20564137; PMCID: PMC4295788; Prébet T, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol. 2011 Aug 20;29(24):3322-7. doi: 10.1200/JCO.2011.35.8135. Epub 2011 Jul 25. PMID: 21788559; PMCID: PMC4859209.

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

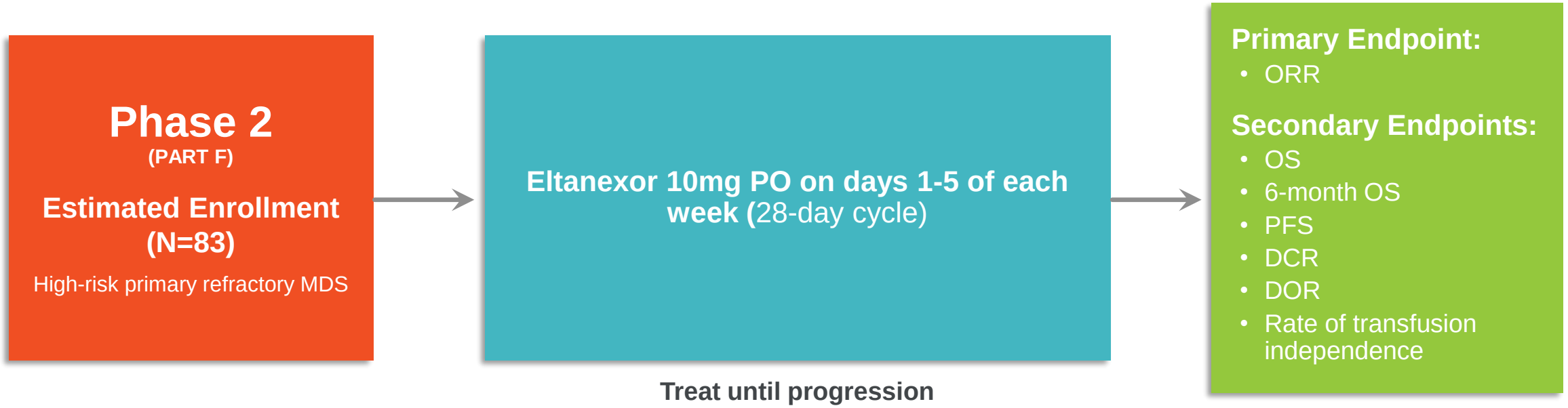
- No approved drugs and historical overall survival (OS) 4-6 months in HMA refractory MDS patients
- **Single-agent eltanexor demonstrated median OS of 9.9 months**
- **Single-agent eltanexor demonstrated 53% ORR**

	Total N=15
Overall Response Rate (mCR + HI)[2,3]	**53%**
Treatment duration (weeks)	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.

1. Lee, Sangmin, et al. EHA 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



DCR, disease control rate; DOR, duration of response; MDS, myelodysplastic syndrome; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; Karyopharm Therapeutics Inc. Clinical Study Protocol. Version 7.0. KCP-8602-801.

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

What is MF?

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

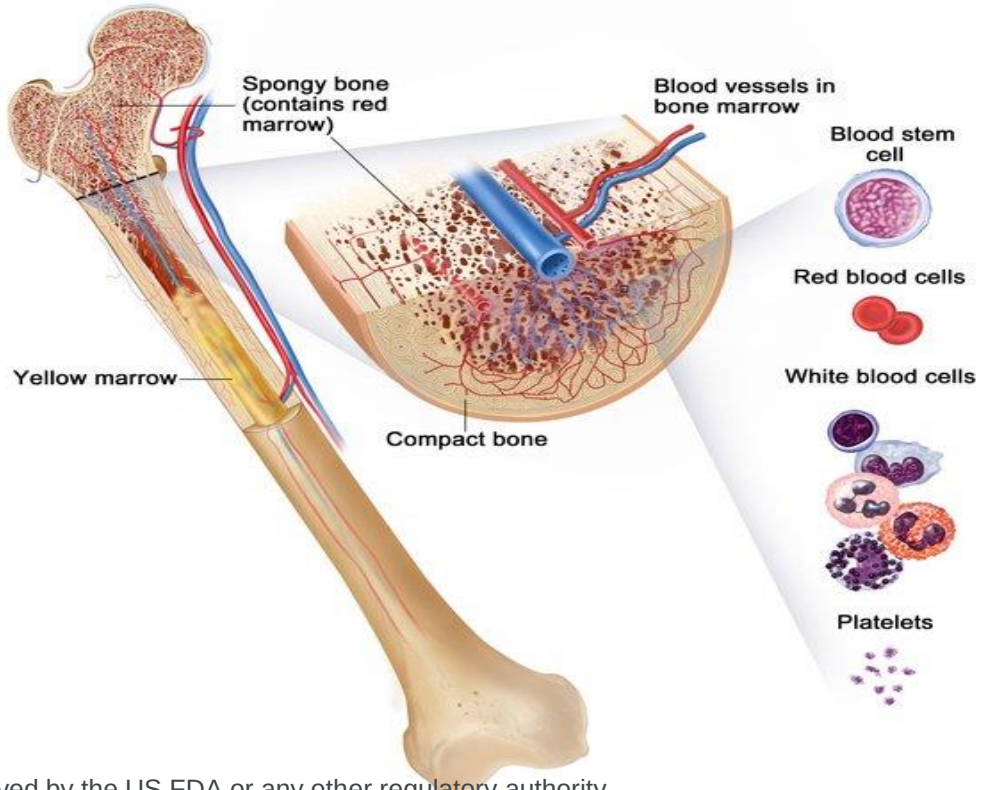
Treatment Landscape

- 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
- **No other class of drugs approved in ruxolitinib-refractory MF**

Opportunity and Unmet Need

- Prognosis in ruxolitinib-refractory disease is poor, with an expected median survival of ~14 months[2]
- Prevalence of **16,000-18,500 in the US**[3]

It is estimated that ~5,000 cases of relapsed MF occur in the US annually[1]

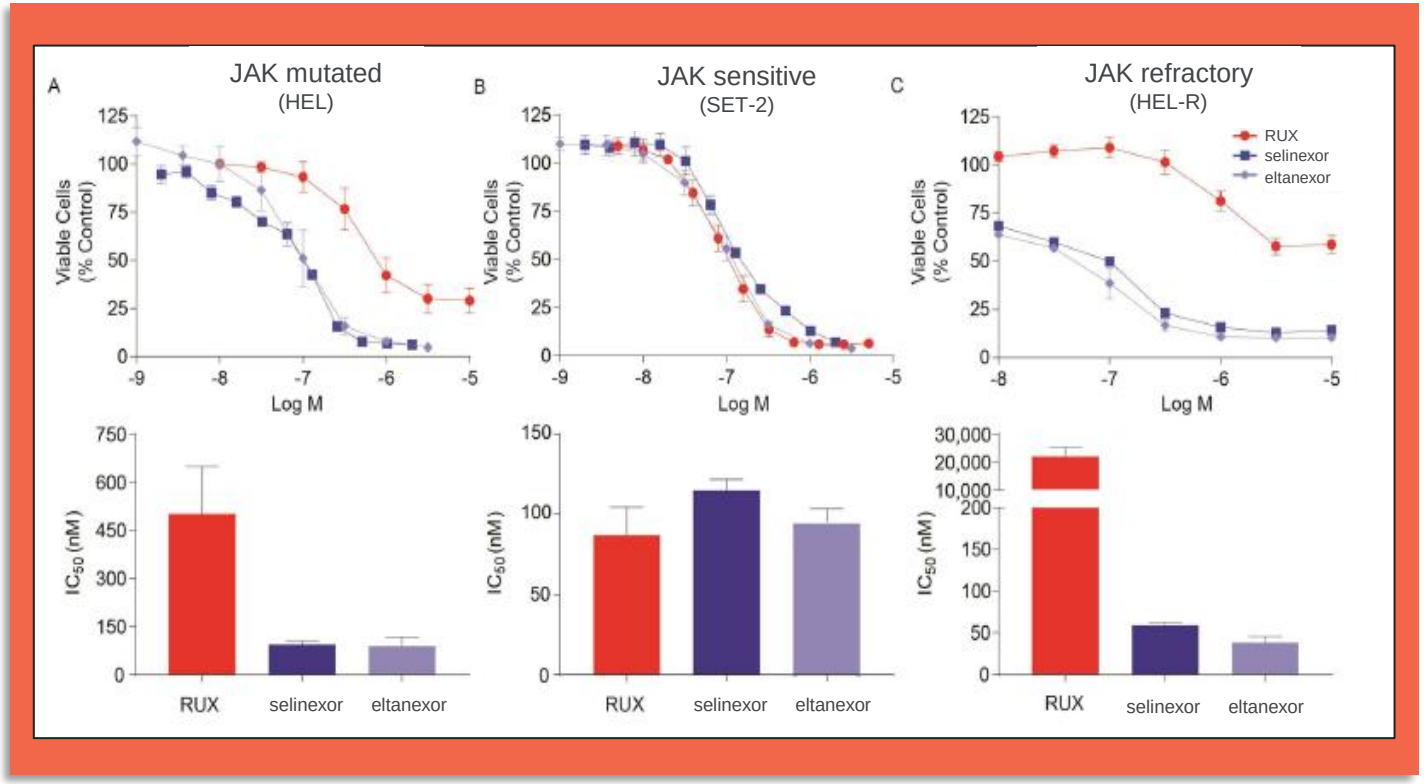


The safety and efficacy of selinexor in myelofibrosis not been established and has not been approved by the US FDA or any other regulatory authority.

1. https://my.clevelandclinic.org/health/diseases/15672-myelofibrosis. 2. Newberry KJ , et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. Blood . 2017;130:1125–1131; Palandri F, et al. Life after ruxolitinib: reasons for discontinuation, impact of disease phase, and outcomes in 218 patients with myelofibrosis. Cancer . 2019;26:1243–1252; Kuykendall AT, et al. Between a rux and a hard place: evaluating salvage treatment and outcomes in myelofibrosis after ruxolitinib discontinuation. Ann Hematol . 2018;97:435–441. 3. Clarivate/ DRG Myelofibrosis Niche & Rare Disease Landscape & Forecast (Nov 2020).

Preclinical Data Supports Potential for Selinexor in MF[1]

Investigator-sponsored Phase 2 clinical data submitted to ASH 2021 for presentation

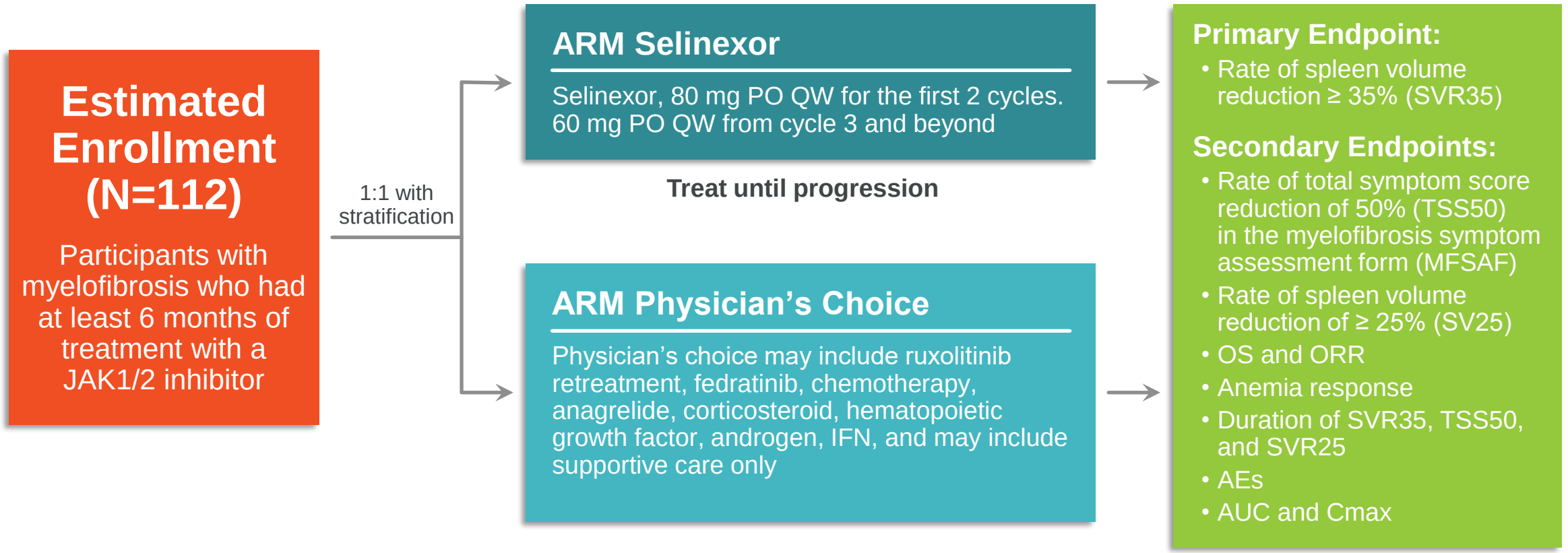


- In preclinical studies, inhibition of nuclear-cytoplasmic transport by selinexor or eltanexor reduced survival of cells expressing JAK^{2V617F}
- Potential for broad applicability in both newly diagnosed and ruxolitinib-exposed patients

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] Yan et al, Clinical Cancer Research 2019.

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



AEs, adverse events; AUC, area under the curve; Cmax, maximum concentration; DCR, disease control rate; DOR, duration of response; IFN, interferon; MDS, myelodysplastic syndrome; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; QW, once weekly; Therapeutics Inc. Clinical Study Protocol. Version 7.0. KCP-8602-801.

MICHAEL MASON
Chief Financial Officer

FINANCIAL RESULTS AND GUIDANCE

Third Quarter 2021 Financial Results

Statements of Operations ($ millions)	3Q 2021	3Q 2020
Total Revenue	**$37.7**	**$21.3**
XPOVIO Net Sales	26.7	21.3
License and Other Revenue	11.0	-
Total Operating Expenses	**$81.5**	**$68.4**
Cost of Sales	0.6	0.4
Research and Development Expenses	45.8	37.0
Selling, General & Administrative Expenses	35.1	31.0
Net Loss	**$51.8**	**$53.5**
Net Loss (per share)	**($0.69)**	**($0.73)**

Balance Sheet ($MM)	Sept 30, 2021	Dec 31, 2020
Cash, Cash Equivalents, Restricted Cash and Investments	**$209.3**	**$276.7**

2021 Financial Guidance

- Non-GAAP Combined R&D and SG&A Expenses[1] of $270-290 million
- Cash runway expected to be sufficient to fund planned operations into mid-2023

1. Excludes stock-based compensation expense. This outlook can only be provided on a non-GAAP basis because Karyopharm cannot reliably predict without unreasonable efforts the timing or amount of the factors that substantially contribute to the projection of stock compensation expense.

Richard Paulson
Chief Executive Officer

CLOSING REMARKS

Continued Focus on Delivering Results and Advancing the Pipeline

YTD 2021 Achievements

1. Accelerated growth in multiple myeloma; positioning XPOVIO as standard of care in 2L+
2. Attained conditional marketing approval in Europe and UK for penta-refractory STORM population
3. EMA validation of BOSTON MAA (Type II variation)
4. First patients dosed in two new company-sponsored trials evaluating selinexor either alone or in combination with approved agents in melanoma and myelofibrosis
5. First patient dosed in new company-sponsored trial evaluating eltanexor alone and in combination with INQOVI® in patients with MDS
6. Secured $60M additional funding

Future Near-Term Milestones

1. Continue to enhance commercial capabilities and increase US XPOVIO sales
2. EMA decision expected in 2L+ based on BOSTON study[1]
3. Initiation of Phase 3 study evaluating selinexor + pomalidomide in patients with multiple myeloma
4. SIENDO Phase 3 top-line data to be announced
5. Additional selinexor data in various hematologic indications submitted to ASH 2021
6. Host virtual investor day to outline strategic imperatives and pipeline priorities

1. Approval of the BOSTON study will fulfill the confirmatory study requirement for STORM conditional approval.

Q&A SESSION