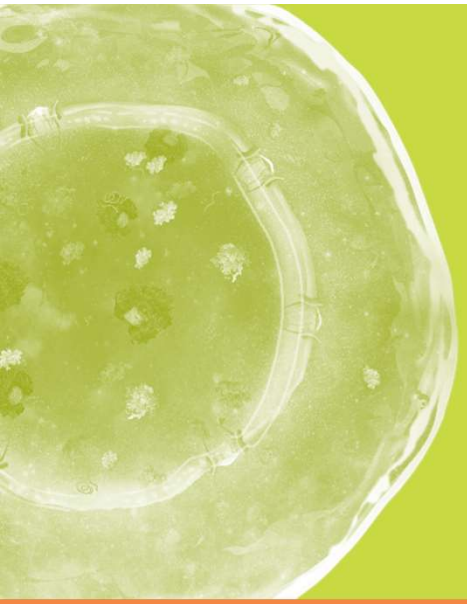
Karyopharm® Therapeutics

A Commercial-Stage Pharmaceutical Company Pioneering Novel Cancer Therapies

August 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 financial guidance for full year 2022; 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 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 June 30, 2022, which was filed with the Securities and Exchange Commission (SEC) on August 4, 2022, 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.



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

Karyopharm® Therapeutics

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

Expanding on multiple myeloma foundation

Continued expansion of XPOVIO by driving commercial excellence, moving into earlier lines and global approvals

Focused mid- and late-stage clinical pipeline

Multiple catalysts expected near and mid-term, including pursuing approvals in endometrial cancer, myelofibrosis and myelodysplastic syndromes

Strong executive leadership

Strengthened leadership team with key appointments in 2022

Well-capitalized

Cash runway into early 2024

Second Quarter 2022 and Recent Highlights

Strong Financials with Increasing Revenues and Cost Savings in 2022

2Q22 Total Revenue

$39.7M; 76% YoY growth

- Expanding global approvals driving growing levels of license and other revenue
- Cost management to match a focused pipeline

Expanding on Multiple Myeloma Foundation Globally

2Q22 Net Product Revenue

$29.0M; 44% YoY growth

- Full EU approval for NEXPOVIO expanding indication to 2L+
- Launches in mainland China by Antengene and Canada by Forus

XPOVIO® NEXPOVIO®

Continue to Advance Clinical Pipeline in Core Indications

Selinexor in Myelofibrosis

- Orphan drug designation by FDA
- Completing enrollment in Phase 1/2 frontline study in **myelofibrosis** for interim analysis in 2H22; encouraging initial data from selinexor + ruxolitinib combo presented at ASCO 2022

Eltanexor in MDS

- FDA Fast Track designation[1] and EU orphan drug designation
- Completed enrollment for interim analysis in relapsed refractory **MDS** Phase 2 study

1. For the development of eltanexor as a monotherapy for the treatment of patients with relapsed or refractory intermediate, high-, or very high-risk MDS per IPSS-R

Prioritized and Targeted Core Programs Focused on Driving Improved Patient Outcomes in Areas of High Unmet Need

MULTIPLE MYELOMA

Enabling **a 'Class Switch' in Earlier Lines of Therapy** to continue improving patient outcomes

ENDOMETRIAL CANCER

Potential to be the **First Maintenance-Only Treatment Option** for patients whose tumors are p53 wild-type

MYELOFIBROSIS

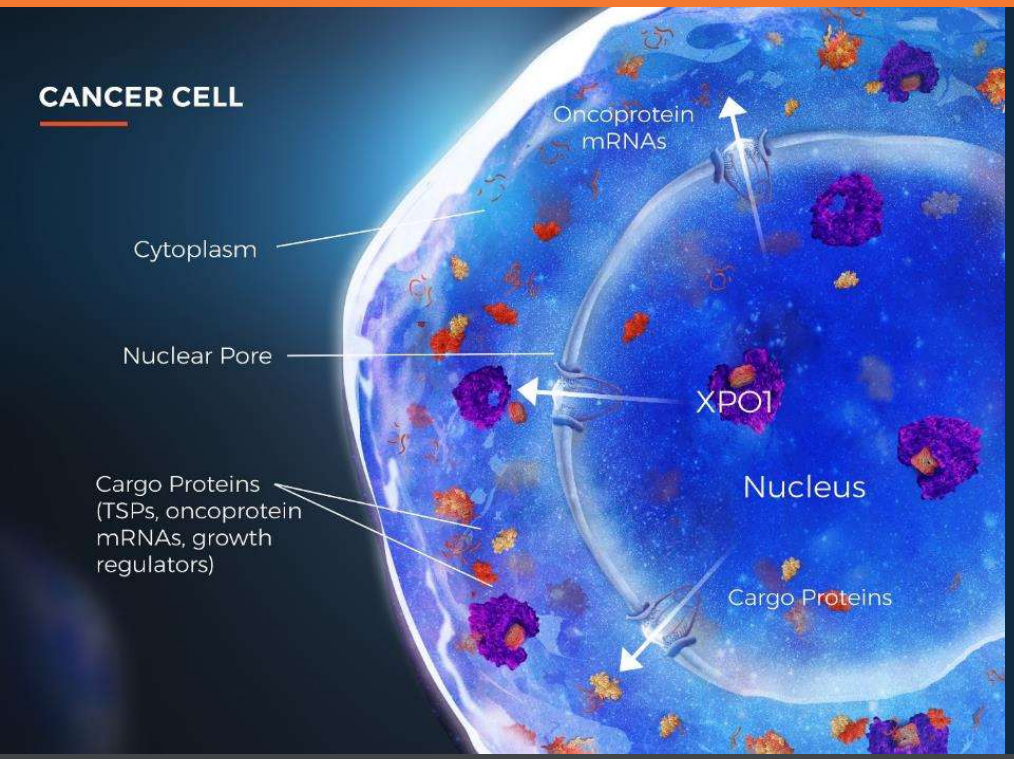
Potential to improve patient outcomes in **frontline and relapsed/refractory MF**

MYELODYSPLASTIC SYNDROMES

Potential to improve patient outcomes in **frontline and relapsed/refractory MDS**

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

Karyopharm is the Leader in Selective Inhibition of Nuclear Export (SINE), a Novel Mechanism that is Broadly Applicable and Foundational to Cancer Biology[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

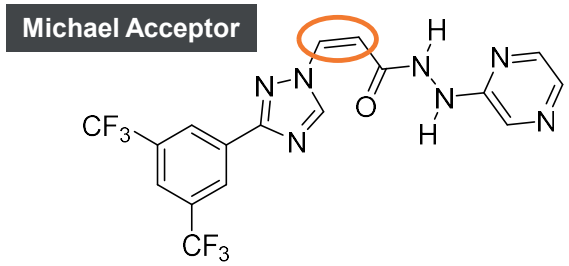
INHIBITION OF XPO1 IMPACTS TUMOR CELLS VIA 3 CORE MECHANISMS

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

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

Two Differentiated, Complementary Novel SINE Compounds

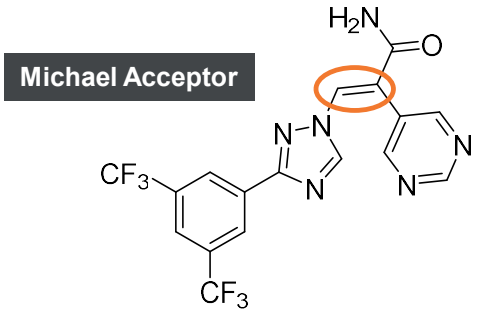
SELINEXOR



- ✓ Only approved, first-in-class SINE compound which leverages once or twice a week dosing
- ✓ Selectively forms a covalent bond with XPO1 (Michael reaction)
- ✓ FDA approved in Multiple Myeloma and DLBCL
- ✓ Future development builds upon strong foundation to date with programs in both Solid Tumors and Hematology
- ✓ Prioritization of clinical development in endometrial cancer (p53 wild type) and myelofibrosis

Focused on areas where a **highly potent** XPO-1 impact is needed

ELTANEXOR



- ✓ Composition inclusive of a more activated Michael Acceptor for binding with XPO1
- ✓ Minimal CNS penetration that allows for frequent dosing (5 days a week)
- ✓ Potentially compelling efficacy as a single agent in HMA-refractory MDS
- ✓ Strong rationale for further development in both Solid Tumors and Hematology

Focused on areas where **continuous** XPO-1 Inhibition needed

Progressing Focused Pipeline Across Cancers With High Unmet Needs

	Regimen	Indication	Study Name	Early Stage	Mid Stage	Late Stage	Commercial
XPOVIO® (selinexor)	w/dexamethasone	Multiple myeloma (penta-refractory)	STORM				
	w/bortezomib + dexamethasone	Multiple myeloma (2L+)	BOSTON				
	monotherapy	DLBCL (R/R)	SADAL				
SELINEXOR	w/R-GDP	DLBCL (R/R)	XPORT-DLBCL-030[1]				
	monotherapy	Endometrial cancer (maintenance)	SIENDO				
	monotherapy	Endometrial cancer (maintenance; p53 wild-type)					
	w/pomalidomide + dexamethasone	Multiple myeloma (2L+)	XPORT-MM-031[2,3]				
	w/multiple approved agents	Multiple myeloma (relapsed/refractory)	STOMP[4]				
	monotherapy	Myelofibrosis (previously treated)	XPORT-MF-035				
	w/ruxolitinib	Myelofibrosis (treatment naïve)	XPORT-MF-034[5]				
ELTANEXOR	monotherapy	Myelodysplastic syndromes (refractory)	KCP-8602-801				
	+ hypomethylating agents	Myelodysplastic syndromes (newly diagnosed)	KCP-8602-801				

hematologic cancer solid tumor cancer Coming soon

1. XPORT-DLBCL-030 is a Phase 2/3. 2. Versus elotuzumab, pomalidomide, and dexamethasone. 3. Sponsored by European Myeloma Network. 4. STOMP has a total of 11 arms; 1 arm still enrolling, 7 arms with patients still in follow up, 3 arms closed. **5.** XPORT-MF-034 is a Phase 1/2.

MULTIPLE MYELOMA

Selinexor Improves Outcomes for Patients with Relapsed Multiple Myeloma

What is Multiple Myeloma?

- Cancer of the plasma cells and the **second most common blood cancer** in the world[1]
- Malignant plasma cells produce a paraprotein (an inactive antibody known also as M-protein) that adversely affects bone marrow, bones, and kidneys

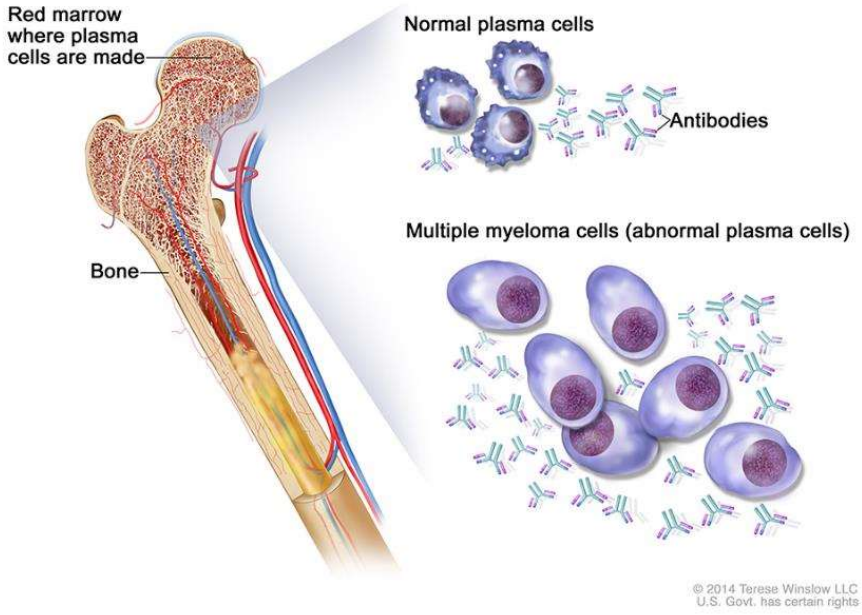
Treatment Landscape

- Following first line progression, **treatment decisions are based on physician and patient choice** rather than clear treatment guidelines
- Current standard of care is to **switch drug classes** once a regimen stops responding

Opportunity and Unmet Need

- Retrospective analyses of currently approved combination regimens demonstrate **poor outcomes for patients with multiple myeloma refractory to prior daratumumab (anti-CD38 mAb)** treatment, including low ORRs and short PFS
- **25%** patients have multiple myeloma with high-risk cytogenetics and poorer outcomes with currently available therapies[3]

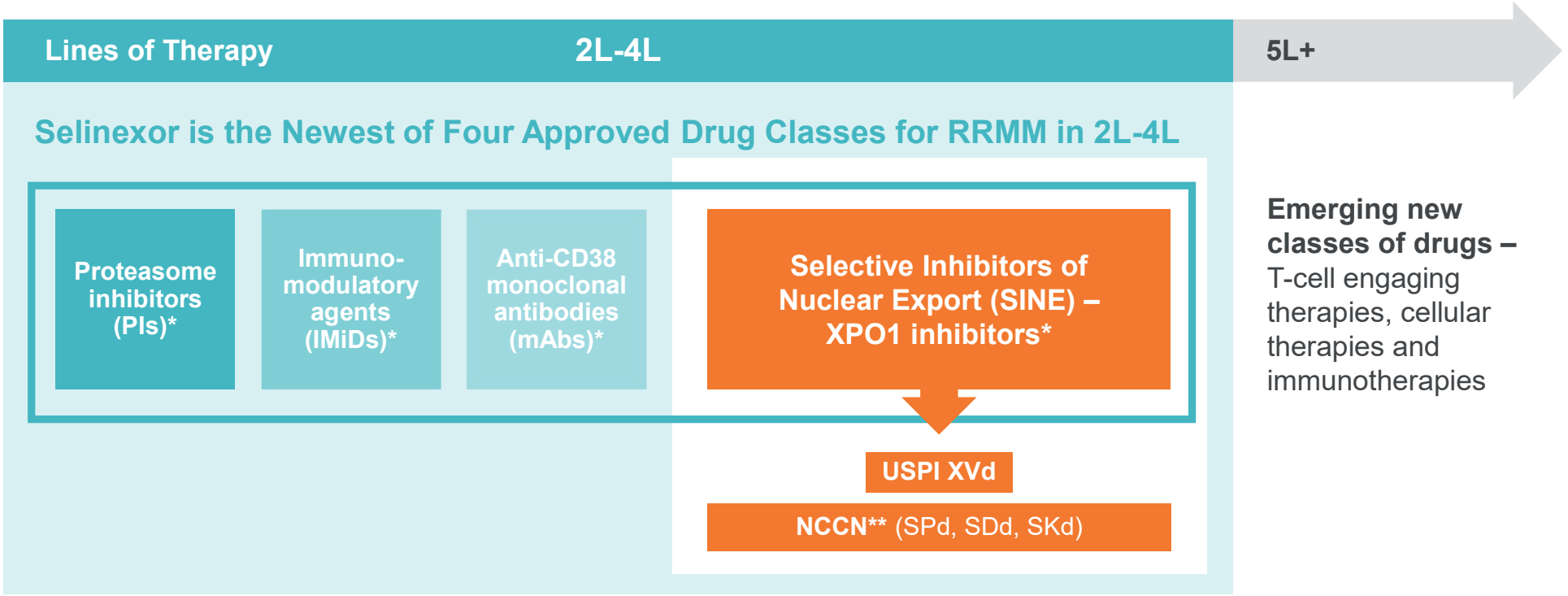
Affects ~47,000 patients in the US in 2L+[2]



1. International Myeloma Foundation. What is Multiple Myeloma? https://www.myeloma.org/what-is-multiple-myeloma. Accessed November 2021. **2.** Clarivate/DRG Forecast & Landscape for MM (2022) **3.** Am J Hematol. 2020;95:548–567.

XPOVIO: 4th Novel Class of Therapy for 2L–4L RRMM post anti-CD38

XPOVIO Provides a Class Switch and Combinatorial Optionality to Future Regimens



Safety and efficacy of selinexor in combinations other than XVd and Xd have not been established and have not been approved by the US FDA or any other regulatory authority.

XPOVIO combinations other than XVd and Xd will not be promoted by Karyopharm, but may be considered for future indication updates.

* +dexamethasone
** NCCN Guideline inclusion for SPd, SDd and SKd

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

Approval Date: July 2019	Approval Date: Dec 2020	Ongoing/Completed
1st approval in MM Dose: **160 mg (80 mg twice weekly)**	2nd approval in MM Dose: **100 mg once weekly**	Phase 1/2 study in MM Dose range: **60-100 mg once weekly**
Xd STORM	**XVd** BOSTON	**SPd, SKd, SDd** STOMP
Phase 2b, single-arm, open-label, multicenter study Patients with penta-refractory MM	Phase 3, 2-arm, active comparator-controlled, open-label, multicenter study After at least 1 prior therapy in MM	Phase 1/2, open-label, multicenter study Patients with RRMM (dose escalation/expansion)

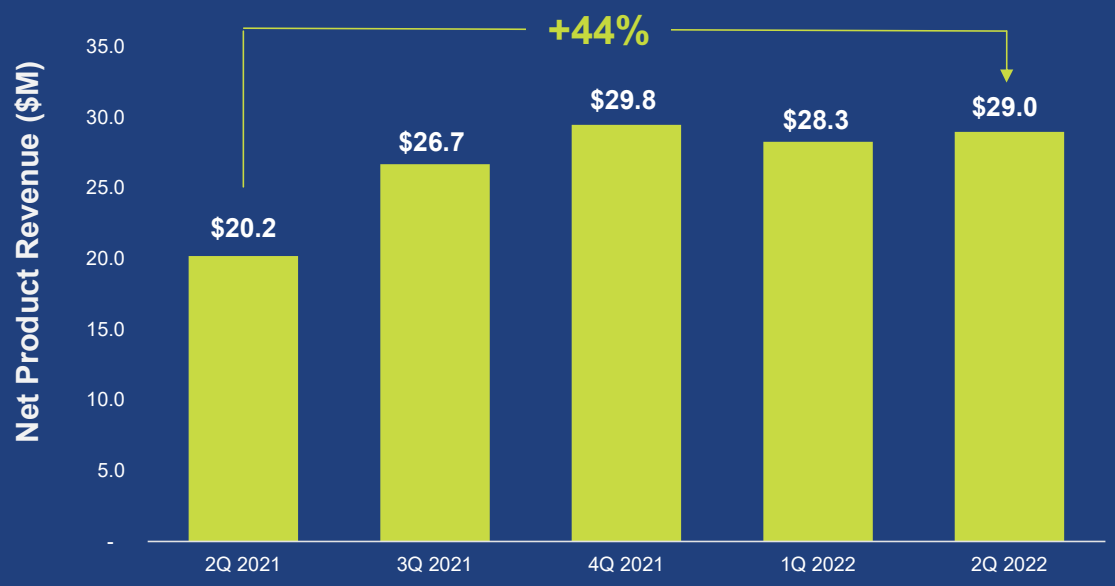
Once Weekly *(previously twice weekly)* | **Lower Dose** *(previously a higher dose)* | **XPOVIO-based Triplets** *(previously a doublet)* | **Earlier Lines** *(previously only in later lines)* | **Supportive Care** *(active symptom management)*

*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: 2Q 2022

Net Product Revenue up 44% YoY Driven by Growth in 2L-4L



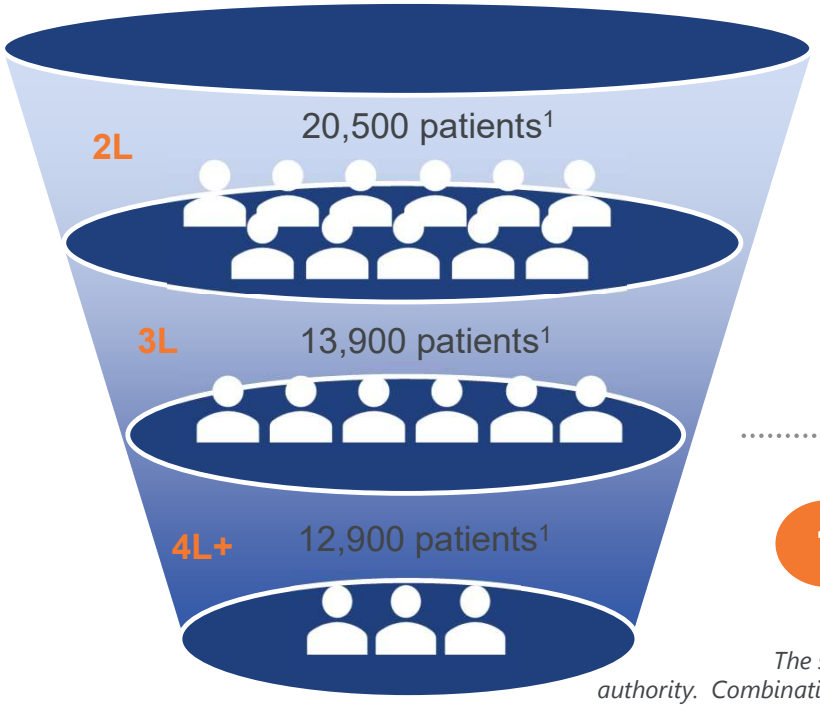
2Q 2022 Highlights

- Net product revenue up 44% for 2Q22 vs 2Q21
- Increasing use of XPOVIO in earlier lines; > 50% of patients in second to fourth lines[1]
- QoQ decline in refills, impacted by slow down of new patient starts (NRx) in January and February due to COVID-19, followed by NRx recovery in 2Q22.
- Continued strong growth in Community driven by positive shift in perception
  - Intensified competition in later lines in Academic centers
  - Future growth expected to come from increased penetration in Community setting and uptake in earlier lines

1. Komodo Health Claims Data from June 2022

Striving to be a Standard of Care in 2L+, Driving Sustainable and Long-Term Growth

~47,000 US patients/year in 2L+[1]



Karyopharm's focus

2

XVd

BOSTON approval in 2L+ (Dec 2020)

3

SPd

Advancing all-oral triplet into Phase 3 targeting 2L+

1

Xd

STORM approval in 4L+ (July 2019)

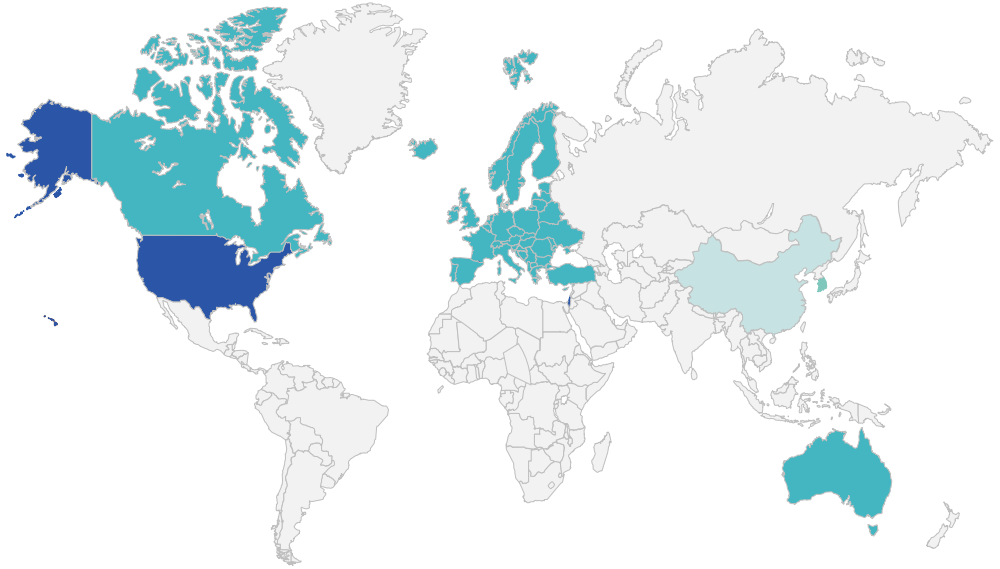
The safety and efficacy of SPd has not been established and has not been approved by the FDA or any other regulatory authority. Combinations other than XVd and Xd are not promoted by Karyopharm but may be considered for future indication updates.

1. Clarivate/DRG Forecast & Landscape for MM (2022)

Full EMA Approval Received for NEXPOVIO® Expanding Indication to 2L+

XPOVIO® / NEXPOVIO® Now Approved in 39 Countries

Country/Region	Indication(s)	Partner
Approvals		
United States		–
Europe[1]		Menarini
UK		Menarini
Mainland China		Antengene
South Korea		Antengene
Australia		Antengene
Singapore		Antengene
Canada		Forus
Israel		Neopharm
Hong Kong		Antengene



- 2L+ multiple myeloma and R/R DLBCL
- 2L+ multiple myeloma
- Penta- or triple-class-refractory multiple myeloma and R/R DLBCL
- Penta- or triple-class-refractory multiple myeloma

1. The 27 countries comprising the European Union, plus Iceland, Norway, Northern Ireland and Lichtenstein.

ENDOMETRIAL CANCER

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.

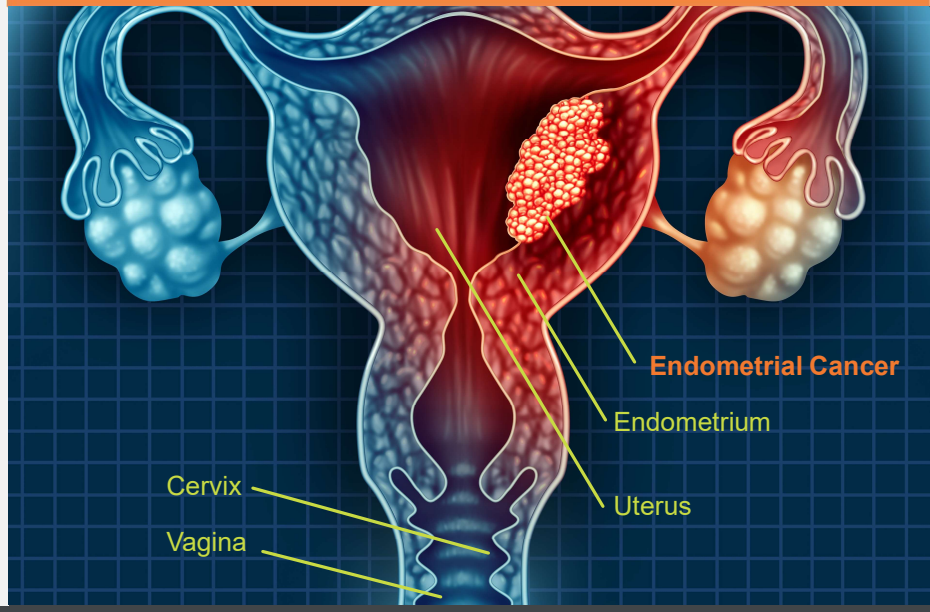
Treatment Landscape

- 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 relapses[4]
- ~50% of patients with advanced or recurrent disease have p53 wild-type tumors[5]

Unmet Need

- Prognosis is poor, with **progression expected within ~4 months[6]** for patients responding to first-line chemotherapy treatment

There will be nearly 66,000 new and 14,000 advanced cases diagnosed in the U.S. in 2022[1] and more than 130,000 cases in Europe[2]



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.

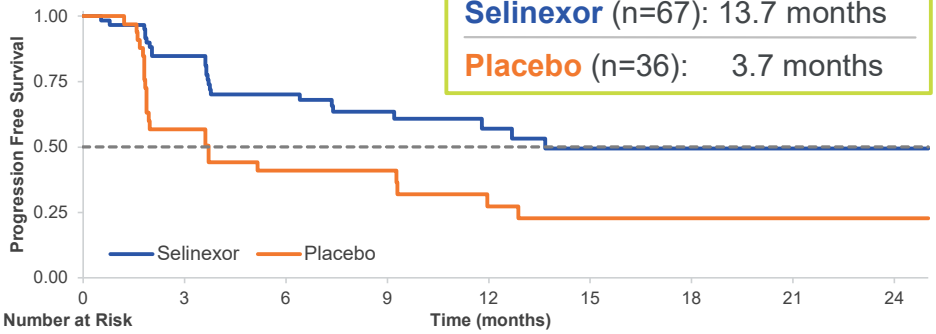
1. American Cancer Society, "About and Key Statistics." Endometrial Cancer. https://www.cancer.org/content/dam/CRC/PDF/Public/8609.00.pdf ; Clarivate/DRG Endometrial Carcinoma Epidemiology Dashboard (2022 figures, pub 2020) 2. International Agency for Research on Cancer, World Health Organization. "Corpus 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. "Mutated p53 portends improvement in outcomes when bevacizumab is combined with chemotherapy in advanced/recurrent endometrial cancer: An NRG Oncology study", Leslie, Kimberly K. et al. Gynecologic Oncology, Volume 161, Issue 1, 113 – 121 6. Based on progression after 6 cycles of CP; Lorusso D. et al, 2015 by American Society of Clinical Oncology

Testing the Hypothesis that p53 Wild-Type has the Potential to be a Robust Biomarker in Endometrial Cancer

Supportive exploratory sub-group analysis from SIENDO trial: patients with Stage IV or first relapse following chemotherapy for at least 12 weeks

Patients with p53 Wild-Type[1,2] Endometrial Cancer (n=103)

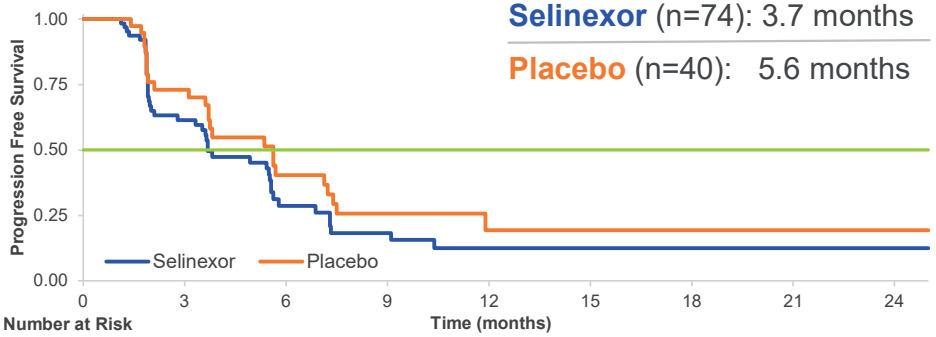
Median PFS
Selinexor (n=67): 13.7 months
Placebo (n=36): 3.7 months



Number at Risk									
Selinexor	67	48	33	24	15	10	7	5	1
Placebo	36	18	11	9	6	5	5	4	2

Patients with p53 Mutant/Aberrant [1,2] Endometrial Cancer (n=114)

Median PFS
Selinexor (n=74): 3.7 months
Placebo (n=40): 5.6 months



Number at Risk									
Selinexor	74	33	11	7	3	1	0	0	0
Placebo	40	25	11	7	3	3	3	2	2

Results from SIENDO Phase 3 evaluating selinexor in patients with advanced or recurrent endometrial cancer unlikely to support sNDA approval. SIENDO Trial AEs were generally manageable with supportive care and dose modifications. Most common Gr ≥3 TRAEs were neutropenia (14%) and fatigue (9%).

Finalizing a CDx Partner Following Productive Dialogue with the FDA

1. p53 WT/MUT status of patients under continued evaluation. 20% of patients on the selinexor arm and 15% of patients on the control arm have pending tumor p53 status. **2.** Preliminary data from pre-specified exploratory subgroup analysis as of the database lock date of January 18, 2022.

Further Exploration of Selinexor in the p53 Wild-Type Population Represents the Potential for a Significant Paradigm Shift for the Treatment of Women with Advanced or Recurrent Endometrial Cancer

Phase 3 SIENDO study

Generated strong hypothesis in patients with p53 wild-type

Addressing a significant unmet need

Currently no FDA approved treatments in the maintenance setting

Significant market opportunity

~14K patients diagnosed with advanced and recurrent endometrial cancer in the U.S. each year[1]

~50% of these patients are p53 wild-type[2]

Supportive Mechanism of Action

Forced retention of p53 wild-type in the cell nucleus by inhibition of XPO1 allows p53 to carry out its tumor suppressor and other regulatory functions

1. Clarivate/DRG Endometrial Carcinoma Epidemiology Dashboard (2022 figures, pub 2020 2. “Mutated p53 portends improvement in outcomes when bevacizumab is combined with chemotherapy in advanced/recurrent endometrial cancer: An NRG Oncology study”, Leslie, Kimberly K. et al. Gynecologic Oncology, Volume 161, Issue 1, 113 – 121

MYELOFIBROSIS

Selinexor Has the Potential to Improve Patient Outcomes in Myelofibrosis

What is Myelofibrosis (MF)?

- Bone marrow cancer that disrupts body's normal production of blood cells
- Causes extensive scarring in bone marrow, leading to enlarged spleen, severe anemia and constitutional symptoms

Treatment Landscape and Unmet Need

- Ruxolitinib is the standard of care for newly diagnosed MF
  - Approximately **40% of patients respond**[2]
  - Responses last up to 4 years
  - Once patients stop responding, the median survival is **only ~14 months**[3] and 5-year survival is ~ 18%[4]
  - In relapsed/refractory patients, an average of ~15%[5] (range <5-30%) of patients will achieve SVR35 with available therapies
- **No other approved class of therapies** other than JAK inhibitors in ~ 10 years

There are ~17,000 Americans living with MF in the US each year[1]

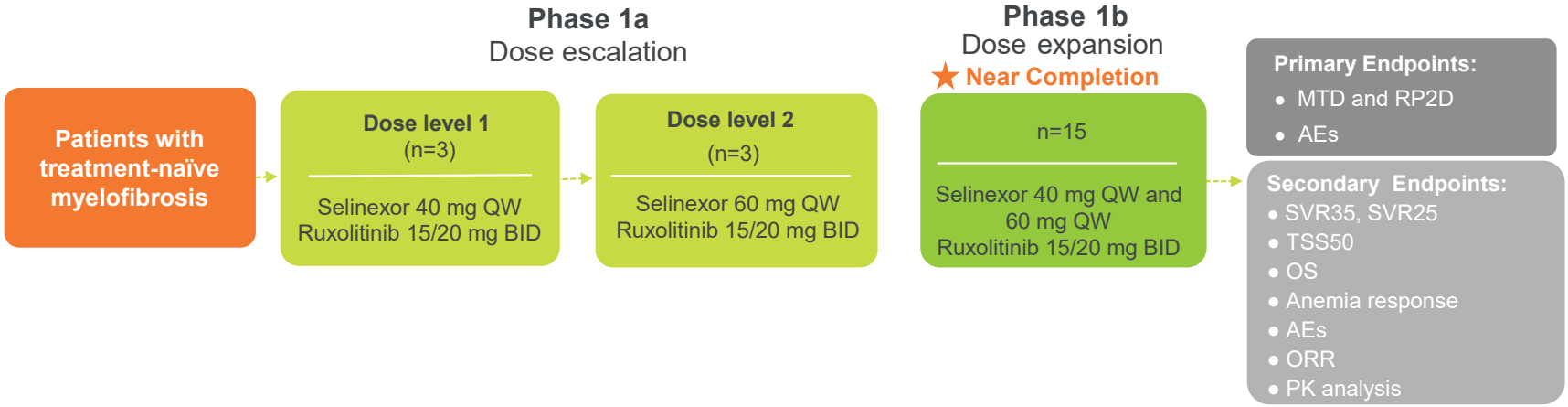
JAK inhibitors are effective in the treatment of MF, but there are significant limitations

✓ **Decrease size of spleen**	✗ Worsening of pre-existing anemia and low platelets
✓ **Improve constitutional symptoms**	✗ Response can be transient or sub-optimal
✓ **Improve QoL**	✗ Limited effect on biology and natural history of the disease

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.

1. Clarivate/DRG Epidemiology Data (2022 figures, pub 2019). **2.** https://www.jakafi.com/myelofibrosis/high-risk-treatment. Accessed Nov 2021. **3.** 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. 4. Price et al. PLoS One. 2014;9(3):e902995 5. Internal assumption based on historical range of <5-30% in the literature; 30% SVR35 rate at EOC6 in patients treated with fedratinib and who received at least 3 months of prior ruxolitinib (JAKARTA-2 updated analysis, Harrison et al 2020. Am J Hematol)

Phase 1/2 Study (XPORT-MF-034[1]) Evaluating Selinexor in Combination with Ruxolitinib in Treatment-naïve Myelofibrosis



AE, adverse event; BID, twice a day; BIW, twice a week; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; QW, once weekly; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SVR25, spleen volume reduction of at least 25%; SVR35, spleen volume reduction of at least 35%; TSS50, total symptom score reduction ≥ 50%.

Preliminary Phase 1 Data Presented at ASCO 2022 and EHA 2022
Update from Phase 1 Expected in 2H 2022

1. NCT04562389

Preliminary Data from Phase 1 Study (XPORT-MF-034)[1] Evaluating Selinexor in Combination with Ruxolitinib in Treatment-naïve Myelofibrosis

SPLEEN RESPONSES AT 12 WEEKS

75% of evaluable patients (6/8) achieved SVR35 at week 12

POSITIVE IMPACTS ON HEMOGLOBIN LEVELS

50% of patients (5/10) maintained stable hemoglobin (± 2g/dL) or improved hemoglobin level (>2g/dL increase) at last follow up

RAPID REDUCTION IN TOTAL SYMPTOM SCORES (TSS)

All evaluable patients (n=7) experienced improvements in symptom scores, with 3/7 patients achieving TSS50 at week 12

SAFETY AND TOLERABILITY

No dose limiting toxicities seen at either dose level. Most common TEAE[2] was nausea, thrombocytopenia and anemia.

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.

1. Ali H, et al. Presented at: American Society for Clinical Oncology 2022 Annual Meeting; June 3-7, 2022. Abstract 7060.
2. Treatment Emergent Adverse Event

No Dose Limiting Toxicities Seen from Selinexor & Ruxolitinib Combination[1]

Treatment Emergent Adverse Events (TEAEs)

TEAEs[a]	Selinexor 40mg or 60mg PO QW + Ruxolitinib PO BID N=15		
Non-Hematologic, n (%)	**Grade 1**	**Grade 2**	**Grades 3 and 4[c]**
Nausea	4 (27)	1 (7)	1 (7)
Dysgeusia	3 (20)	1 (7)	-
Hyponatremia	3 (20)	-	-
Dizziness	3 (20)	-	-
Vomiting	2 (13)	1 (7)	-
Headache	1 (7)	2 (13)	-
Anorexia	1 (7)	-	1 (7)
Atrial Fibrillation	-	-	3 (20)
Failure to thrive[b]	-	-	1 (7)
Pulmonary hypertension	-	-	1 (7)
Tumor lysis syndrome	-	-	1 (7)
Hematologic, n (%)			
Neutropenia	2 (13)	-	3 (20)
Anemia	1 (7)	2 (13)	3 (20)
Thrombocytopenia	1 (7)	1 (7)	4 (27)

The combination of selinexor and ruxolitinib was generally well-tolerated:

- No dose limiting toxicities have been reported thus far at either dose level

Nausea was the most common TEAE

- 40% with majority Grade 1 events

Hematologic adverse events were reversible with dose interruptions and reductions

Dose reductions at last follow-up:

- Ruxolitinib dose reduced in 53% and selinexor dose reduced in 20% of patients

a. TEAEs Grades 1 and 2 that occurred in > 2 patients and TEAEs Grade ≥ 3 that occurred in at least 1 patient.
b. Serious adverse event of “failure to thrive” (related to study treatment) occurred at time of progression to AML and includes other Grade 3 adverse events deemed not related to selinexor or ruxolitinib: abdominal pain, atrial fibrillation, delirium, dysphagia, muscle weakness.
c. Majority of the TEAEs were Grade 3 except for one Grade 4 thrombocytopenia event.

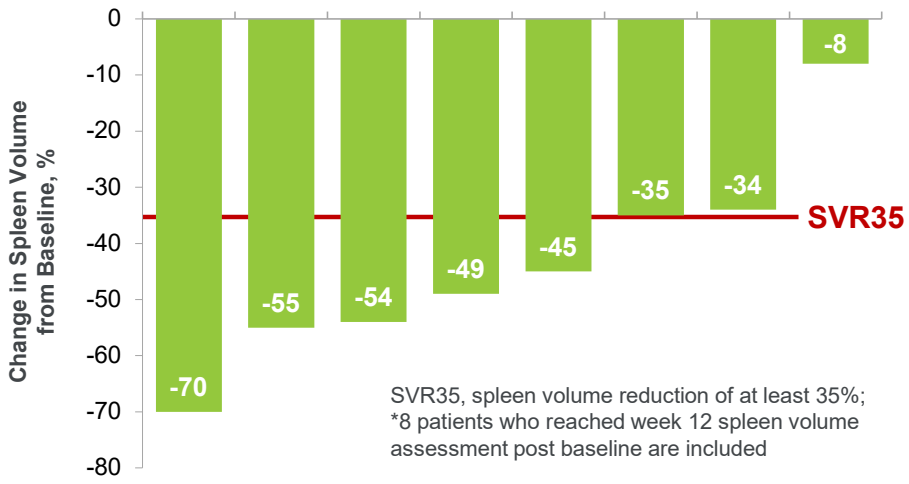
The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the US FDA or any other regulatory authority.

1. Ali H, et al. Presented at: American Society for Clinical Oncology 2022 Annual Meeting; June 3-7, 2022. Abstract 7060.

24

Selinexor & Ruxolitinib Combination Induced Rapid Spleen Responses and Reduction in Symptom Scores at Week 12[1]

Change in Spleen Volume from Baseline at 12 Weeks in All Evaluable Patients* (n=8)

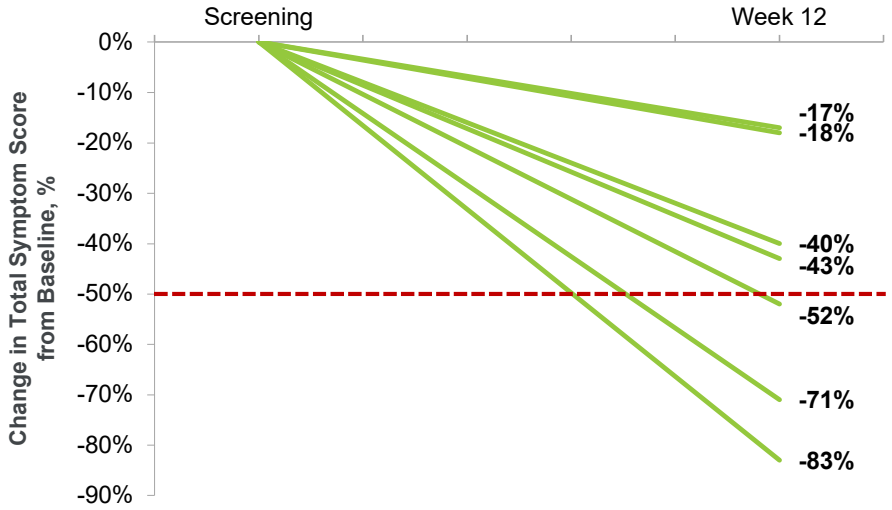


SVR35, spleen volume reduction of at least 35%;
*8 patients who reached week 12 spleen volume assessment post baseline are included

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.

75% (6/8) of Patients Had a ≥35% Reduction in Spleen Volume on Treatment with Selinexor in Combination with Ruxolitinib at 12 weeks

Total Symptom Score at Week 12*



* 7 evaluable patients, who had been at least 12 weeks on treatment and had complete data; Scores from the Myelofibrosis Symptom Assessment Form were collected daily for 5–7 days prior to the start of each cycle. Median score was calculated for each cycle.

1. Ali H, et al. Presented at: American Society for Clinical Oncology 2022 Annual Meeting; June 3-7, 2022. Abstract 7060.

Selinexor Data from Phase 2 ESSENTIAL Study[1]

Single-agent selinexor (60-80mg QW) in patients with myelofibrosis that is refractory or intolerant to JAK1/2 inhibitors

Durable spleen responses:

- 40% achieved SVR35 at ≥24W; 60% achieved SVR25 at ≥24W
- 2-year survival probability: 92%

Positive impacts on hemoglobin levels:

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

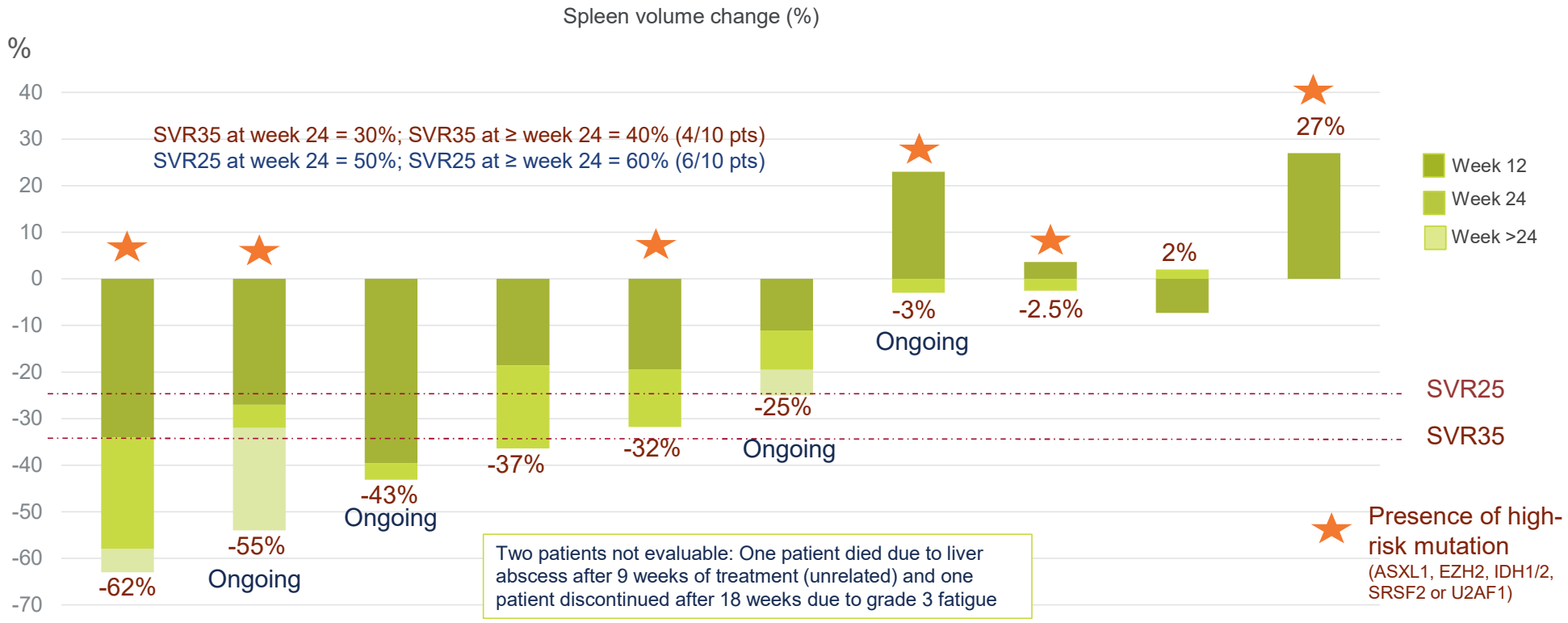
Tolerability and sustainability:

- Most common Gr ≥3 TRAEs: anemia (33%) and fatigue (33%)
- Median treatment duration: 11 months (range 2.8 to 28.8 months)

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.

1. Tantravahi, et al. ASH 2021.

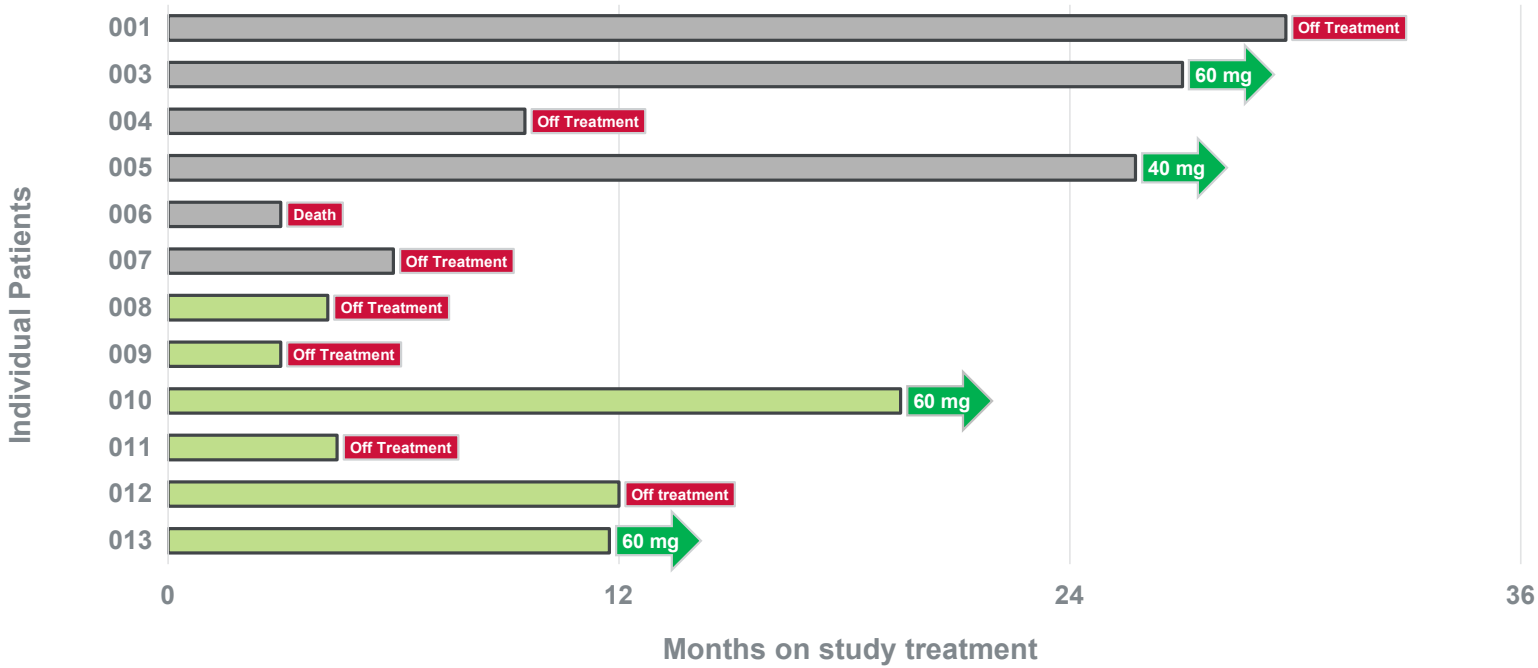
Single-Agent Selinexor Resulted in Sustained Spleen Responses in Refractory MF Patients in ESSENTIAL STUDY[1,2]



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.

1. Tantravahi, et al. ASH 202 2. Data cut-off as of November 2021.

Single-Agent Selinexor Resulted in Durable Responses with Long Term Therapy Documented Beyond Two Years[1]



Median treatment duration 11 months (range 2.8 to 28.8 months)

Selinexor starting Dose

80 mg

60 mg

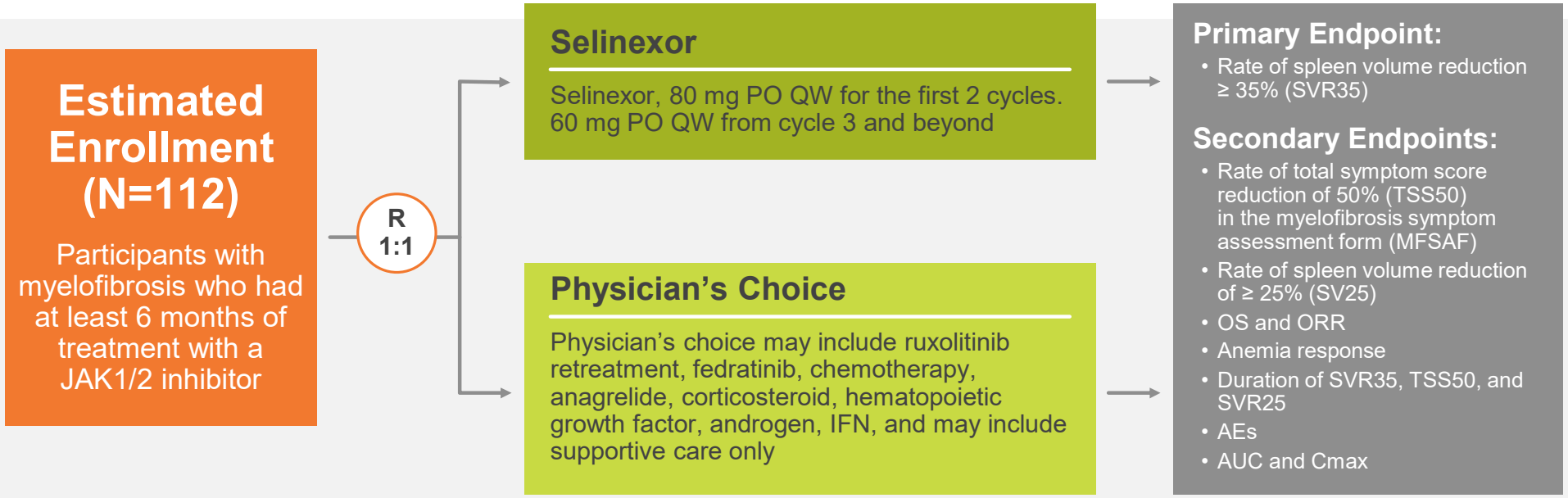
Eight pts (70%) discontinued Selinexor due to: progression (n=2; 1 spleen size progression and 1 AML), changed to another clinical trial (n=2), death (n=1), and toxicity (n=3; 1 fatigue and 2 weight loss)

Data cut of November 2021

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.

1. Tantravahi, et al. ASH 2021.

Phase 2 Study (XPORT-MF-035[1]) Evaluating Single-Agent Selinexor Versus Physician's Choice in Previously Treated MF



Top-line data expected 2H 2023

1. NCT04562870

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;

Selinexor in Myelofibrosis: Key Takeaways

1. **Addressing significant unmet need for patients with MF**
2. **Single-agent selinexor showing robust responses in JAKi-refractory disease with the potential to be an important new class treatment option**
3. **Phase 2 study ongoing in patients with previously treated MF; top-line data expected 2H 2023**
4. **Encouraging preliminary data from selinexor in combination with JAKi in Phase 1/2 in frontline MF presented at ASCO 2022 and EHA 2022. Updated results expected in 2H 2022.**

MYELODYSPLASTIC SYNDROMES

Eltanexor Has the Potential to Improve Survival in Relapsed /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

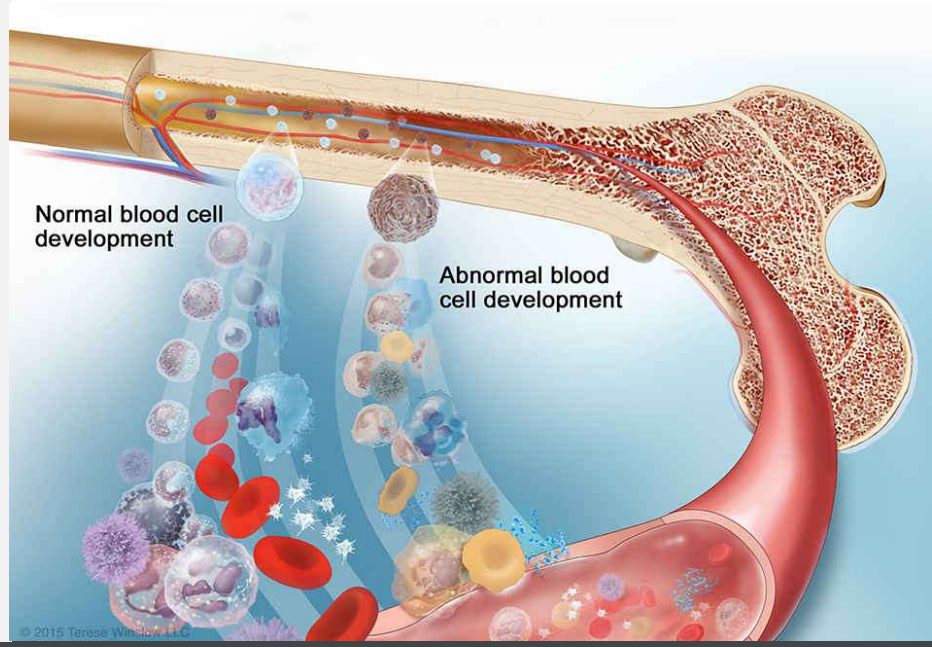
Treatment Landscape

- 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 years[2]

Opportunity and Unmet Need

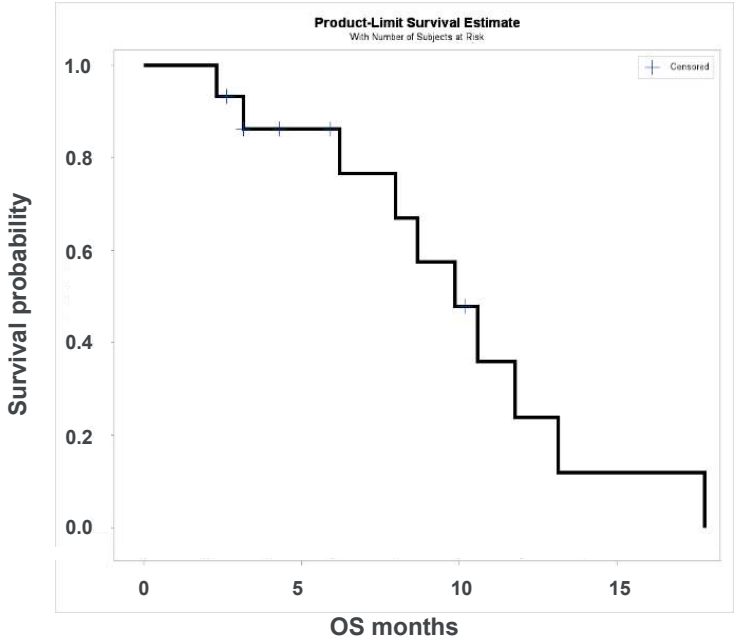
- Prognosis in relapsed/refractory disease is poor, with an **expected survival of 4-6 months**[3,4]
- No currently approved therapies for HMA-refractory disease

~15,000 patients diagnosed with intermediate-to-high risk MDS each year in the US[1]



1. Clarivate/DRG Myelodysplastic-Syndrome-Epidemiology-Dashboard (2022 figures, pub 2020) **2.** Gil-Perez A. Ther Adv Hematol. 2019 doi:10.1177/2040620719847059.. **3.** Jabbour E, Cancer. 2010;116(16):3830-4. **4.** Prébet T. J Clin Oncol. 2011;29:3322-7.

Single-agent Eltanexor Demonstrated Promising Activity Among Patients With HMA Refractory MDS in a Phase 1 Study[1]



- Historical overall survival (OS) of 4-6 months in patients with relapsed/refractory MDS[3]
- **Single-agent eltanexor demonstrated median OS of 9.9 months[2]**

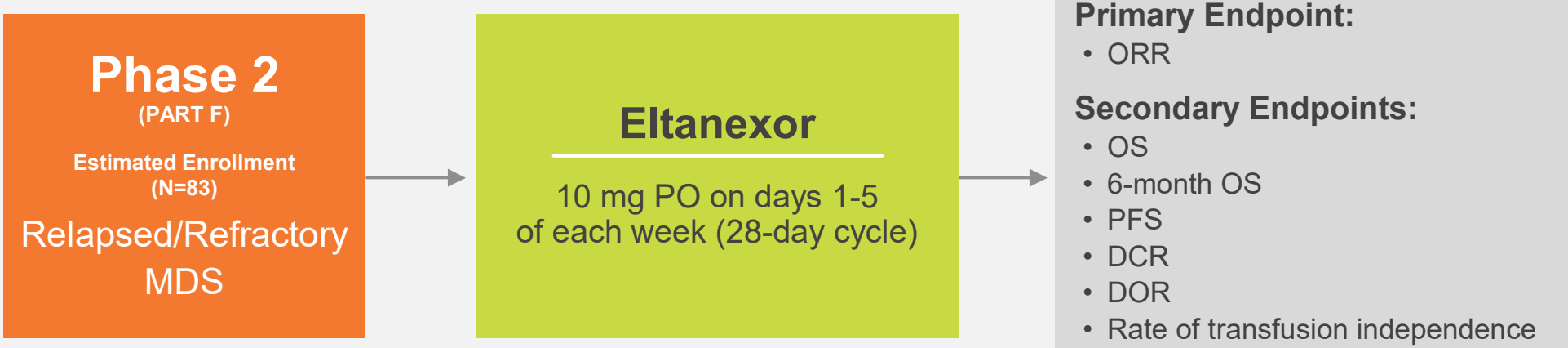
The Grade 3/4 AEs across all patients were anemia (40%), leukopenia (20%), thrombocytopenia without bleeding (20%), decreased appetite/weight (20%), neutropenia (40%): no febrile neutropenia, 1 case of sepsis.

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.)

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. ASH 2021.
2. n=15; 10 patients on 20mg eltanexor and 5 patients on 10mg eltanexor
3. Clavio M, Cancer. 2021;127(12):2015-24.

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



Data from interim analysis expected in 2H 2022

Top-line data expected 1H 2023

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.

Eltanexor in MDS: Key Takeaways

1. **Addressing significant unmet need for patients with relapsed/refractory MDS**
2. **Single-agent eltanexor showing meaningful survival in HMA-refractory MDS**
3. **Phase 2 study ongoing in patients with relapsed/refractory MDS; results from interim analysis expected in 2H 2022 and top-line data in 1H 2023**
4. **Preliminary data from Phase 1 eltanexor in combination with HMAs frontline MDS expected in 2023**

PARTNERSHIPS, FINANCIAL HIGHLIGHTS AND MILESTONES

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 and $ 8.6 million in milestone revenue from Antengene in 4Q21 and 1Q22.

FORUS

- Karyopharm recorded $1.5 million in milestone revenue from Forus in 2Q22 following the approval and launch of Xpovio in Canada.

ANTENGENE

AsiaPac

the MENARINI group

EU & LatAm

NEOPHARM

Israel

FORUS THERAPEUTICS

Canada

2Q 2022 Financial Results

Statements of Operations (millions)	2Q 2022	2Q 2021
Total Revenue	**$39.7**	**$22.6**
XPOVIO Net Product Revenue	29.0	20.2
License and Other Revenue	10.7	2.4
Total Operating Expenses[1]	**$82.6**	**$71.6**
Cost of Sales	0.9	1.1
Research and Development Expenses	44.3	34.0
Selling, General & Administrative Expenses	37.3	36.5
Net Loss	**$(49.1)**	**$(53.6)**
Net Loss per share	**$(0.62)**	**$(0.71)**

Balance Sheet (millions)	June 30, 2022	Dec 31, 2021
Cash, Cash Equivalents, Restricted Cash and Investments	**$172.6**	**$235.6**

Revised 2022 Financial Guidance

- Total Revenue of $155-$165 million
- Net Product Revenue of $120-$130 million, reflecting ~27% growth compared to 2021
- Non-GAAP R&D and SG&A Expenses of $250-$265 million[2]
  - R&D expense in 2022 frontloaded due to clinical trial timing and severance charges
- Cash runway expected to be sufficient to fund planned operations into early 2024

1. Total stock based compensation expense $15.1million in 2Q 2022
2. Karyopharm has not reconciled the full year 2022 outlook for non-GAAP R&D and SG&A expenses to full year 2022 outlook for GAAP R&D and SG&A expenses 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, which is excluded from the full year 2022 outlook for non-GAAP R&D and SG&A

Upcoming Milestones for 2022 and Beyond

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

- Report subgroup and molecular analysis data from SIENDO (ASCO 2022) ✓
- Initiate new registration-enabling Phase 3 study in p53 wild-type (2H 2022)
- Report top-line results (2024)

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

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

Karyopharm® Therapeutics

Thank you!