Karyopharm® Therapeutics

A Commercial-Stage Pharmaceutical Company Pioneering Novel Cancer Therapies

November 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, myelofibrosis, myelodysplastic syndromes, 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.

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Innovation and Patient Focused

Founded in 2008, building on over a decade of research into selective inhibition of nuclear export (SINE) as a novel mechanism of action

Karyopharm® Therapeutics

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

Positioned for Expanded Growth

XPOVIO/ NEXPOVIO
Approved in Multiple Myeloma (MM) and DLBCL

- Expanded global footprint with regulatory approvals in 40 countries
- $155-$165m total revenues expected in 2022
- Moving into earlier lines of therapy in MM

Targeted Expansion of Indications with Focused Clinical Pipeline; Optimizing Dose for Efficacy and Tolerability

- Compelling clinical data in Endometrial Cancer, Myelofibrosis and Myelodysplastic Syndrome (MDS)

Experienced Leadership

- Leadership with a focus on accelerating commercial growth and enhancing mid-to-late stage clinical development

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Third Quarter 2022 and Recent Highlights

Expanding on Multiple Myeloma Foundation Globally with Continued XPOVIO Growth

3Q22 U.S. XPOVIO Net Product Revenue: $32.0M; 20% YoY growth

- Increasing use of XPOVIO in earlier lines with strong growth in the U.S. Community setting
- Recent commercial launches by partner Menarini Group in Germany and Austria following full EU approval for NEXPOVIO in July expanding indication to 2L+

Advancing Clinical Pipeline in Core Indications

Endometrial Cancer (EC): Initiation of Pivotal Phase 3 Study in *TP53* wild-type advanced or recurrent *EC*

- Utilizing Foundation Medicine's tissue-based next generation sequencing test to identify patients whose tumors are *TP53* wild-type

Myelofibrosis: Results from Phase 1 XPORT-MF-034 study evaluating selinexor in combination with ruxolitinib in treatment naïve myelofibrosis to be presented at the 2022 ASH[1] meeting

- Compelling data published in ASH abstract reinforce continued development of the combination
- Received orphan drug designation for selinexor for the treatment of myelofibrosis in Europe[2]

MDS (Eltanexor) Completed enrollment for interim analysis in relapsed/refractory MDS Phase 2

- FDA Fast Track designation[3]
- Waiting for overall survival data maturity and expect to present data in 4Q 2022 / 1Q 2023

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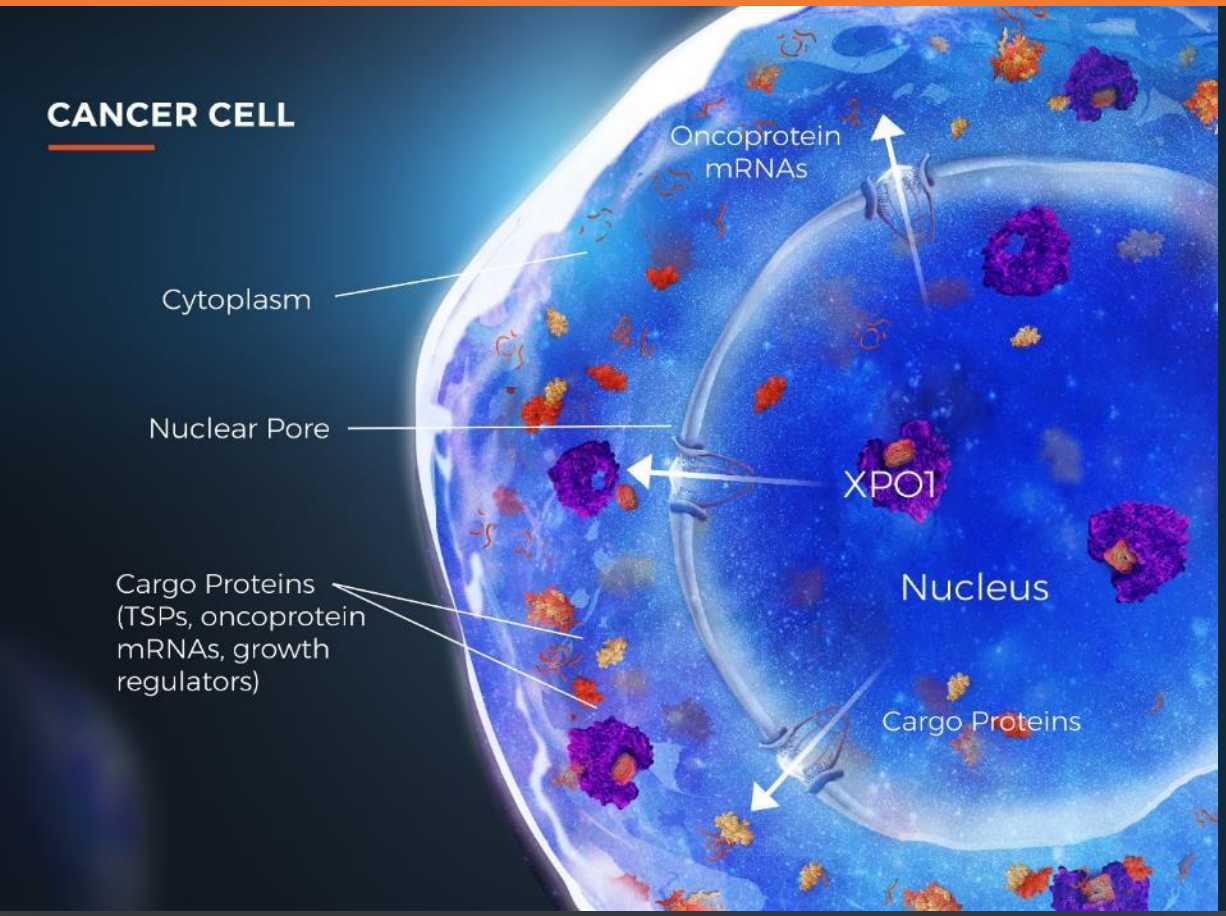
1.American Society of Hematology
2. Received in October 2022
3.Received in July 2022 for the development of eltanexor as a monotherapy for the treatment of patients with relapsed or refractory intermediate, high-, or very high-risk MDS per IPSS-R

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

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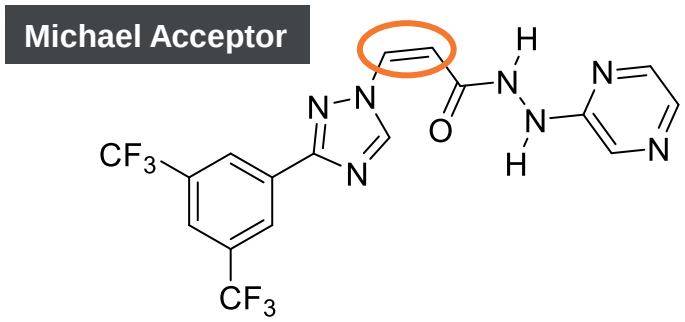
1. Gupta A, et al. J Thorac Oncol. 2017. **2.** Sun Q, et al. Signal Transduct Target Ther. 2016.
3. Gandhi UH, et al. Clin Lymphoma Myeloma Leuk. 2018. **4.** Gravina GL, et al. J Hematol Oncol. 2014

Two Differentiated, Complementary Novel SINE Compounds

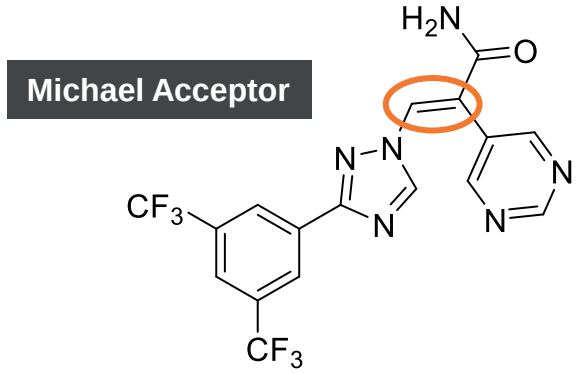
SELINEXOR



- ✓ 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

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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

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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; *TP53* wild-type)	XPORT-EC-042				
	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				

hematologic cancer solid tumor cancer Coming soon

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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

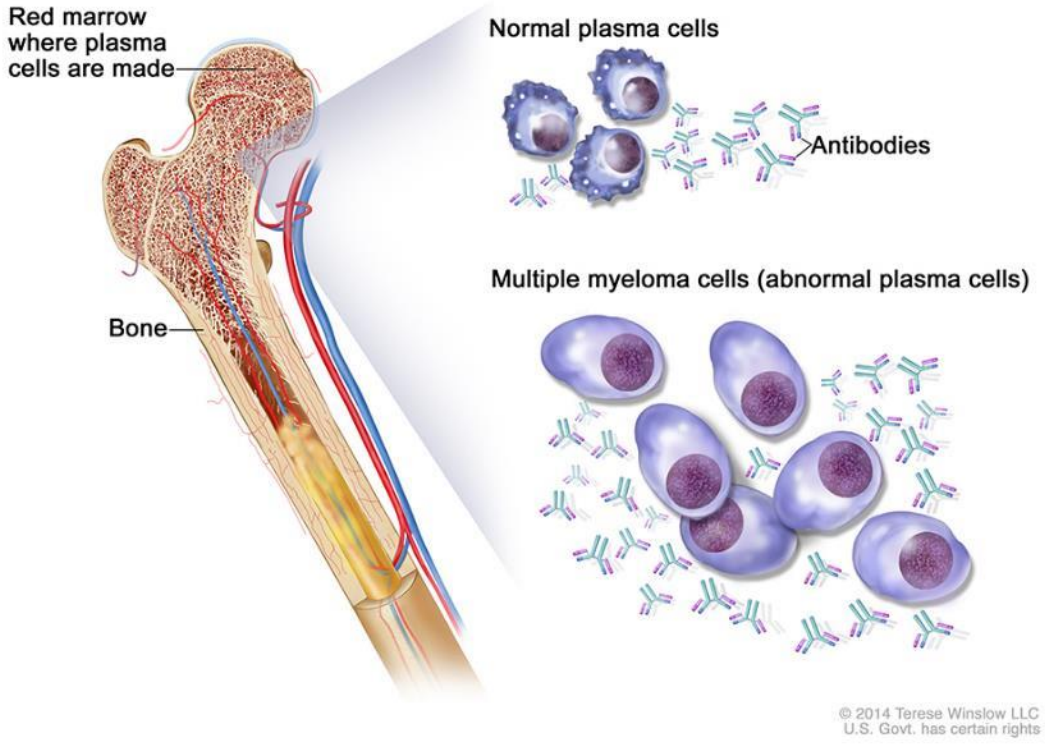
Treatment Landscape

- 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]



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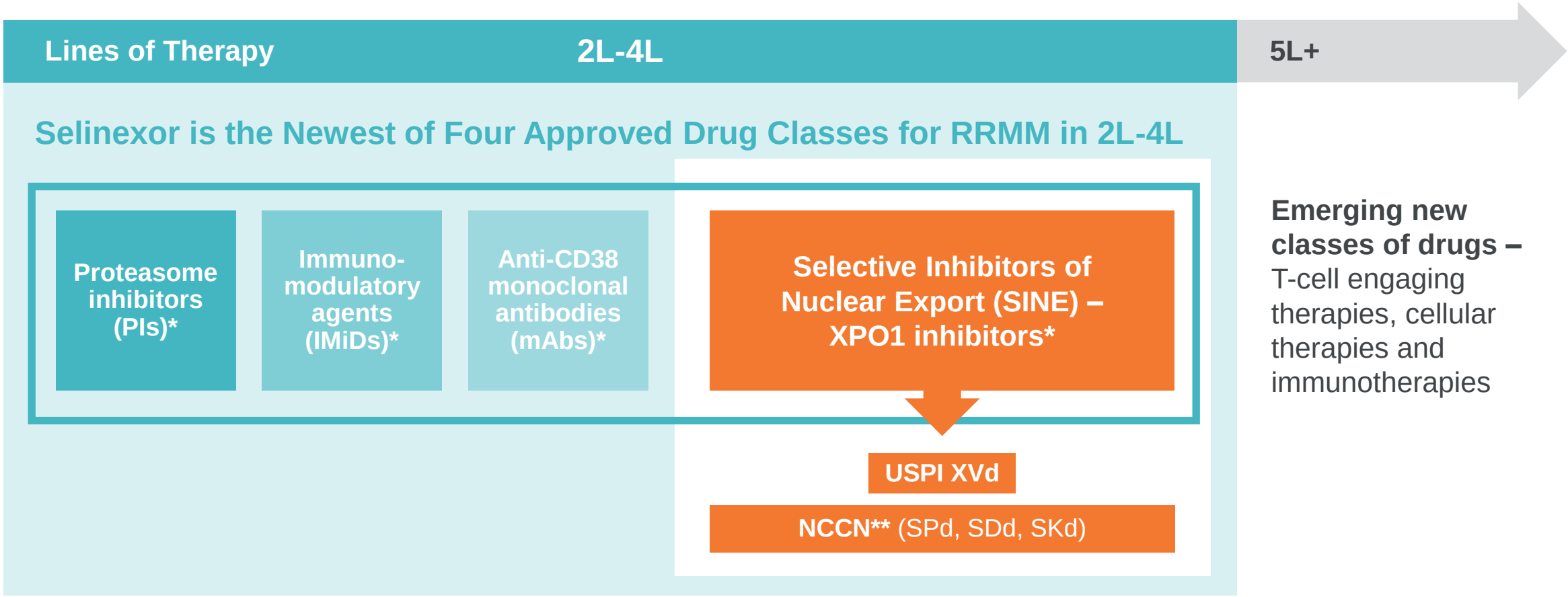
1. International Myeloma Foundation. What is Multiple Myeloma? https://www.myeloma.org/what-is-multiple-myeloma. Accessed November 2021. **2.** Clarivate/DRG Forecast & Landscape for MM (2022) **3.** Am J Hematol. 2020;95:548–567.

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

XPOVIO Provides a Class Switch and Combinatorial Optionality to Future Regimens



Emerging new classes of drugs – T-cell engaging therapies, cellular therapies and immunotherapies

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.

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* +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

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XPOVIO Update: 3Q 2022

Net Product Revenue up 20% YoY Driven by Growth in 2L-4L

3Q 2022 Highlights

- Net product revenue up 20% for 3Q22 vs 3Q21
- Increasing use of XPOVIO in earlier lines; fastest growing brand in 3L multiple myeloma in 1H 2022[1]
- Growth in both new patient starts and refills
- Strong double-digit growth in Community, while Academic business remained stable despite increasing competition in late lines
- Continued improvement in perception and intent-to-prescribe data in 2-4L[2]

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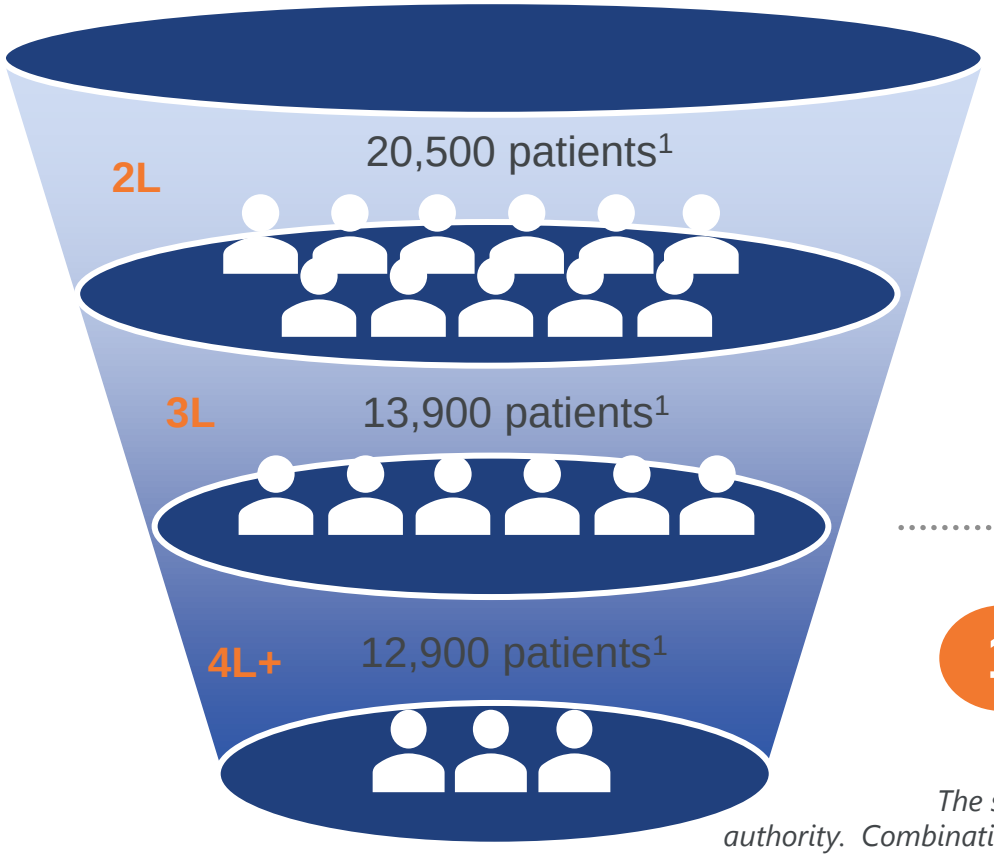
1. Assessed as of August 2022. Based on Komodo claims analysis, comparing U.S. XPOVIO market share in new patients vs other available brands approved in 3L MM in 2021 and 1H 2022
2. Based on internal KPTI Myeloma HCP ATU (healthcare professionals' awareness, trial and usage)

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)

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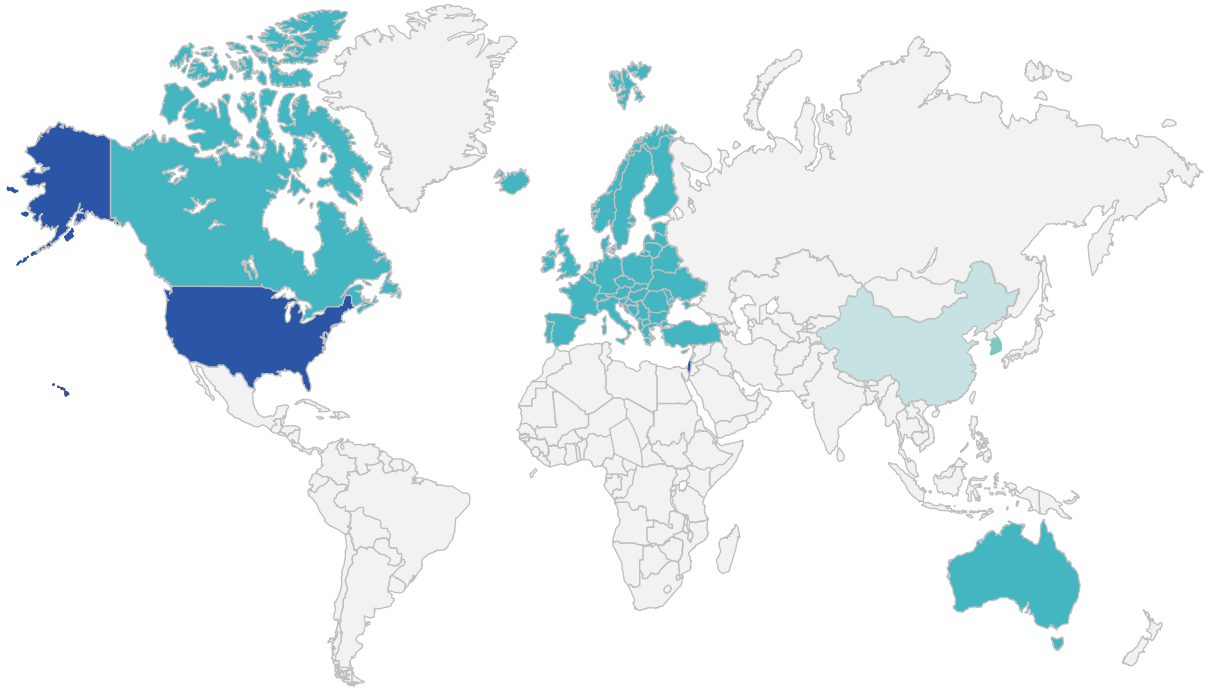
Full EMA Approval Received for NEXPOVIO® Expanding Indication to 2L+

XPOVIO® / NEXPOVIO® Now Approved in 40 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

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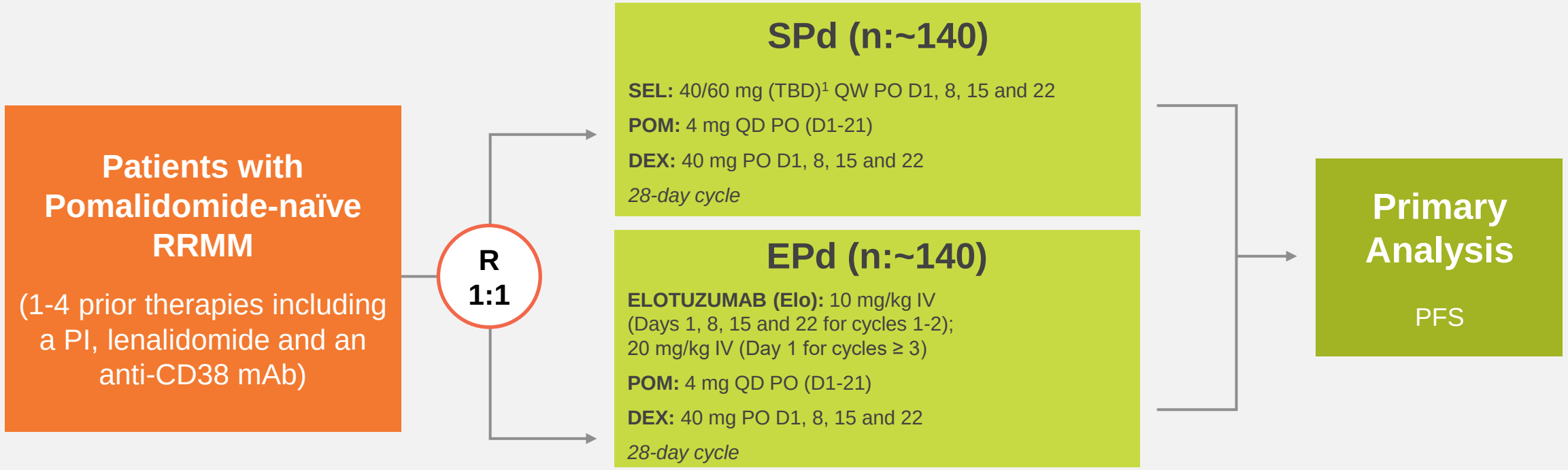
1. The 27 countries comprising the European Union, plus Iceland, Norway, Northern Ireland and Lichtenstein.

Phase 3 Study (XPORT-MM-031) Evaluating Selinexor, Pomalidomide and Dexamethasone (SPd) in Patients with Previously Treated Multiple Myeloma



Top-line data expected in 2H 2024

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1. Final dosing for Selinexor arm to be determined following interim analysis of data from first 60 patients

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.

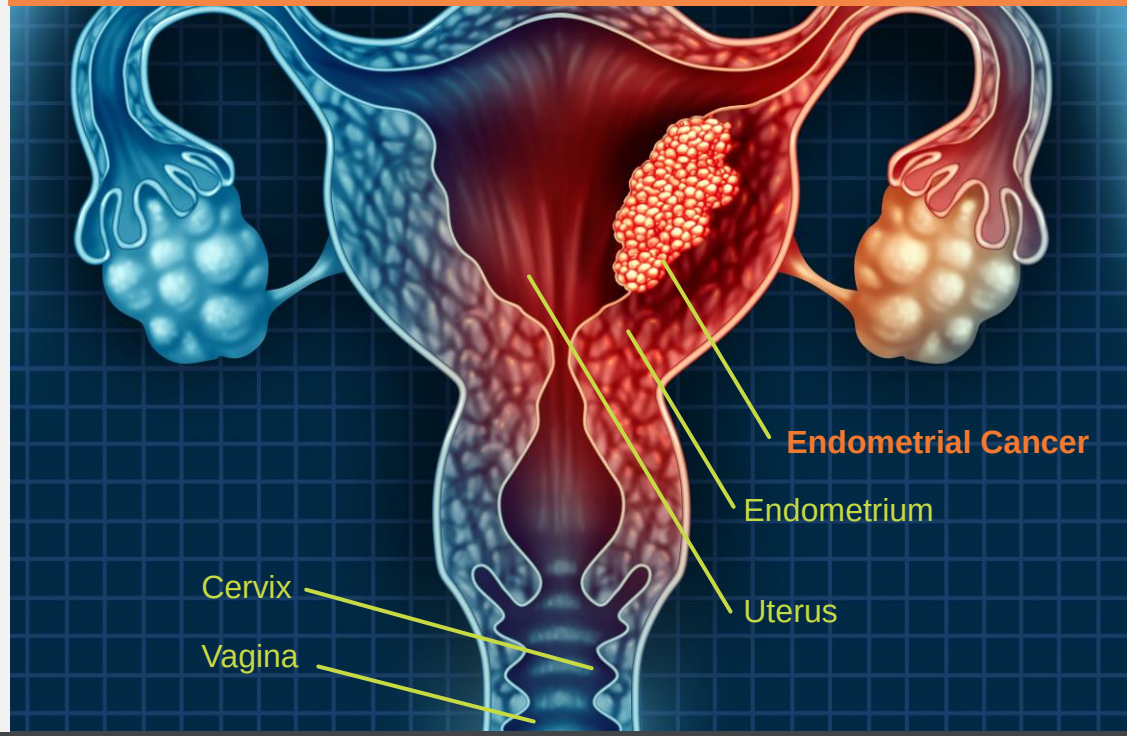
Treatment Landscape

- First-line treatment is chemotherapy (taxane plus platinum), where response rates 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 *TP53* 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 U.S. FDA or any other regulatory authority.

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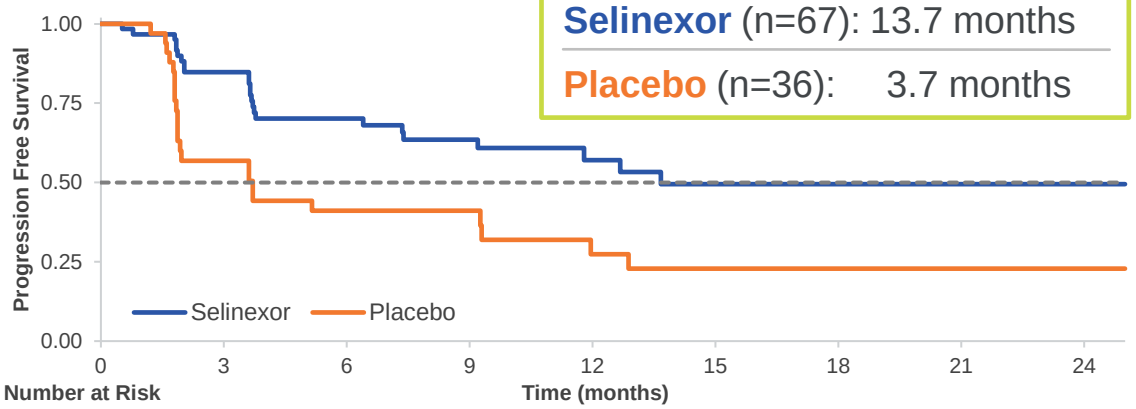
1. American Cancer Society, “About and Key Statistics.” Endometrial Cancer. https://www.cancer.org/content/dam/CRC/PDF/Public/8609.00.pdf ; Clarivate/DRG Endometrial Carcinoma Epidemiology Dashboard (2022 figures, pub 2020) 2. International Agency for Research on Cancer, World Health Organization. “Corpus 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

TP53 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 *TP53* Wild-Type[1,2] Endometrial Cancer (n=103)

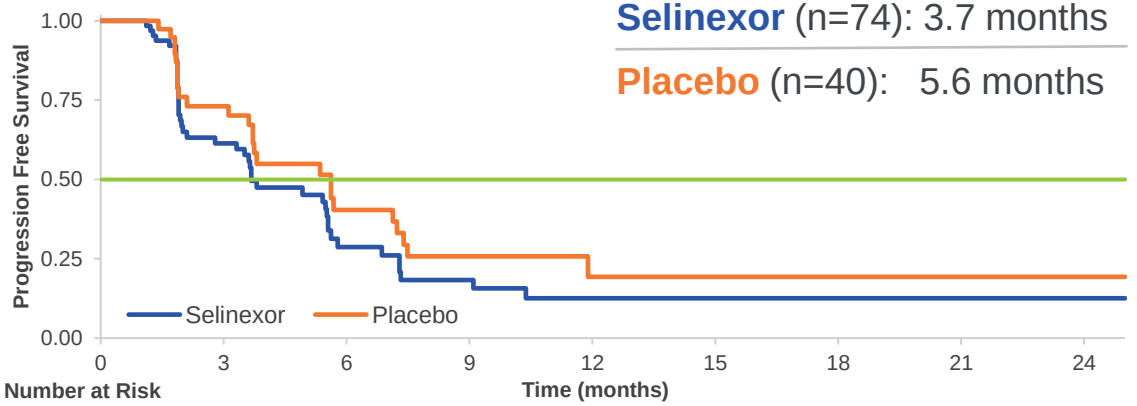
Median PFS
Selinexor (n=67): 13.7 months
Placebo (n=36): 3.7 months



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 *TP53* Mutant [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

SIENDO Trial adverse events (AEs) were generally manageable with supportive care and dose modifications. Most common Gr ≥3 treatment related AEs were neutropenia (14%) and fatigue (9%).

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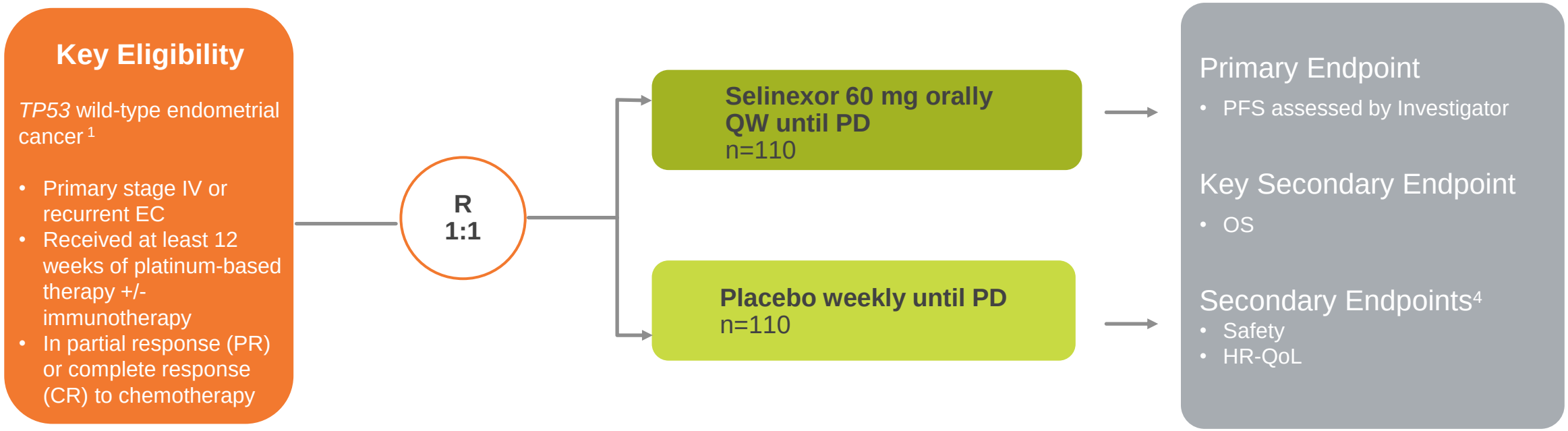
1. TP53 WT/MUT status of patients under continued evaluation. 20% of patients on the selinexor arm and 15% of patients on the control arm have pending tumor TP53 status. **2.** Preliminary data from pre-specified exploratory subgroup analysis as of the database lock date of January 18, 2022.

Initiated Global Phase 3 Registrational Study; *TP53* Mutation Status Will Be Assessed by Foundation Medicine[1]

XPORT-EC-042 Global Phase 3, Randomized, Double-Blind, Trial of Selinexor as Maintenance Therapy for Patients with *TP53* Wild-type, Advanced or Recurrent Endometrial Cancer (N=220)

Study in Collaboration with ENGOT[2] and GOG[3]



- HR-QoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PD, progressive disease; QW, every week

1. Utilizing Foundation Medicine's tissue-based next generation sequencing test to identify *TP53* status
2. European Network for Gynaecological Oncological Trial groups; 3. Gynecologic Oncology (GOG) Foundation
4. Selected secondary endpoints

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Potential for Significant Paradigm Shift for the Treatment of Women with Advanced or Recurrent *TP53* Wild-Type Endometrial Cancer

Phase 3 SIENDO study

Generated strong hypothesis in patients with *TP53* wild-type EC

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 have *TP53* wild-type EC[2]

Supportive Mechanism of Action

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

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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 spleen volume reduction ≥ 35% (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 U.S. 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 U.S. FDA or any other regulatory authority.

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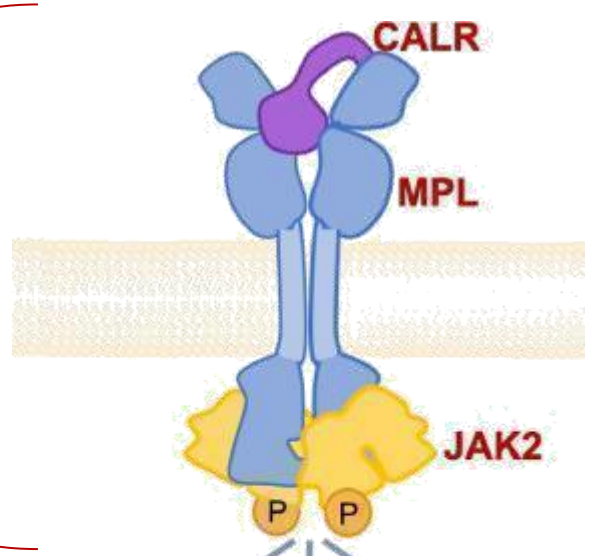
1. Clarivate/DRG Epidemiology Data (2022 figures, pub 2019). **2.** https://www.jakafi.com/myelofibrosis/high-risk-treatment. Accessed Nov 2021. **3.** Newberry KJ , et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. Blood . 2017;130:1125–1131; Palandri F, et al. 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)

Selinexor Can Inhibit Multiple Targets of the JAK/STAT Pathway, Enabling Independent Suppression of MF cells and Potentially Complementing the Function of JAKi's[1,2,3,4,5]

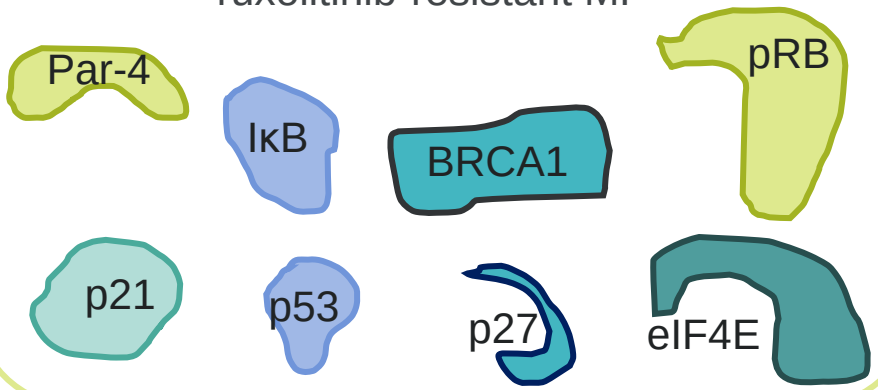
MF is driven by **upstream mutations** of *JAK2, CALR* or *MPL*



Downstream pathways are activated by the upstream mutations

The AKT, STAT and ERK pathways contain XPO1 cargo proteins

Additional XPO1 cargos proteins that regulate cell growth and survival may be important, especially in ruxolitinib-resistant MF



XPO1

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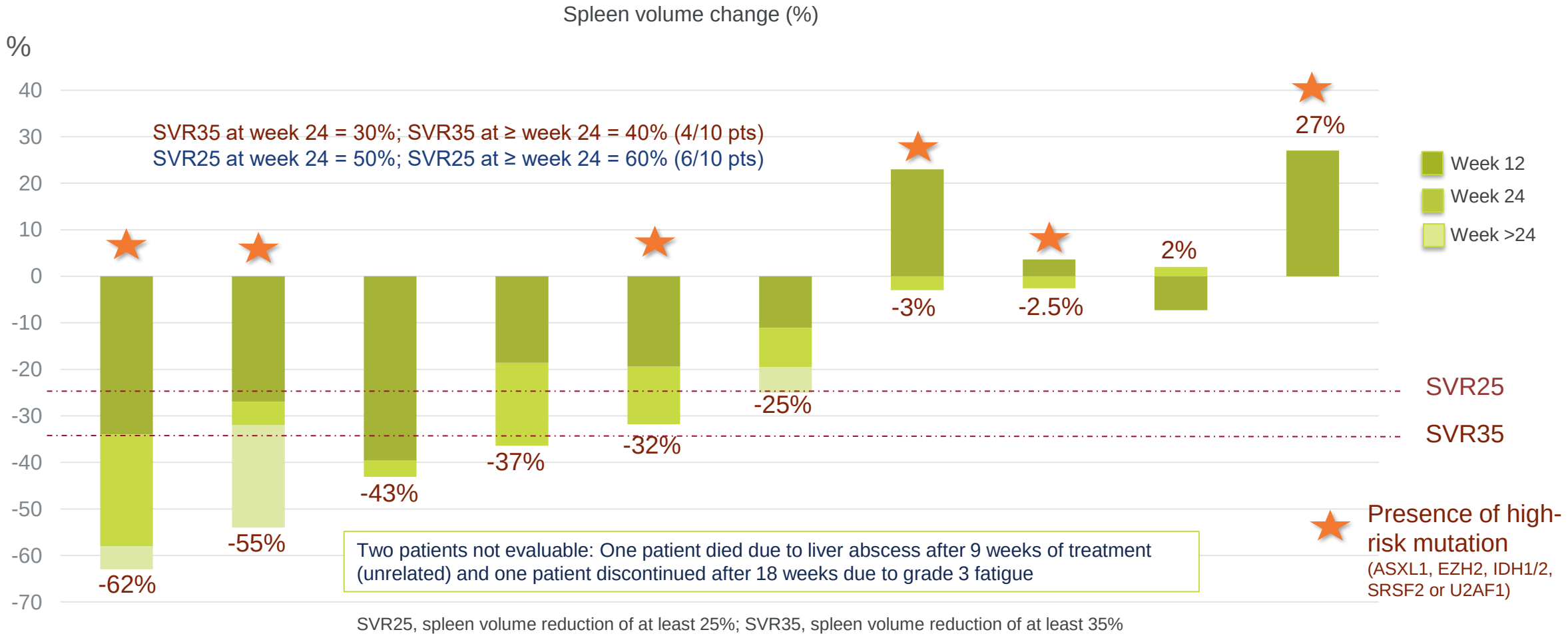
1. Exp Hematol (105):2-9, Jan. 01, 2022
2. XPO1 Cargo references: https://doi.org/10.7554/eLife.11466; http://prodata.swmed.edu/LRNes/IndexFiles/namesGood.php
3. Zhong et al., Leukemia. 2014 May;28(5):1158-63 ; 4. Muqbil et al., Cancer Lett. 2016 Dec 28;383(2):309-317
5. Cheng et al., Mol Cancer Ther. 2014;13(3):675-686

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



SVR25, spleen volume reduction of at least 25%; SVR35, spleen volume reduction of at least 35%

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

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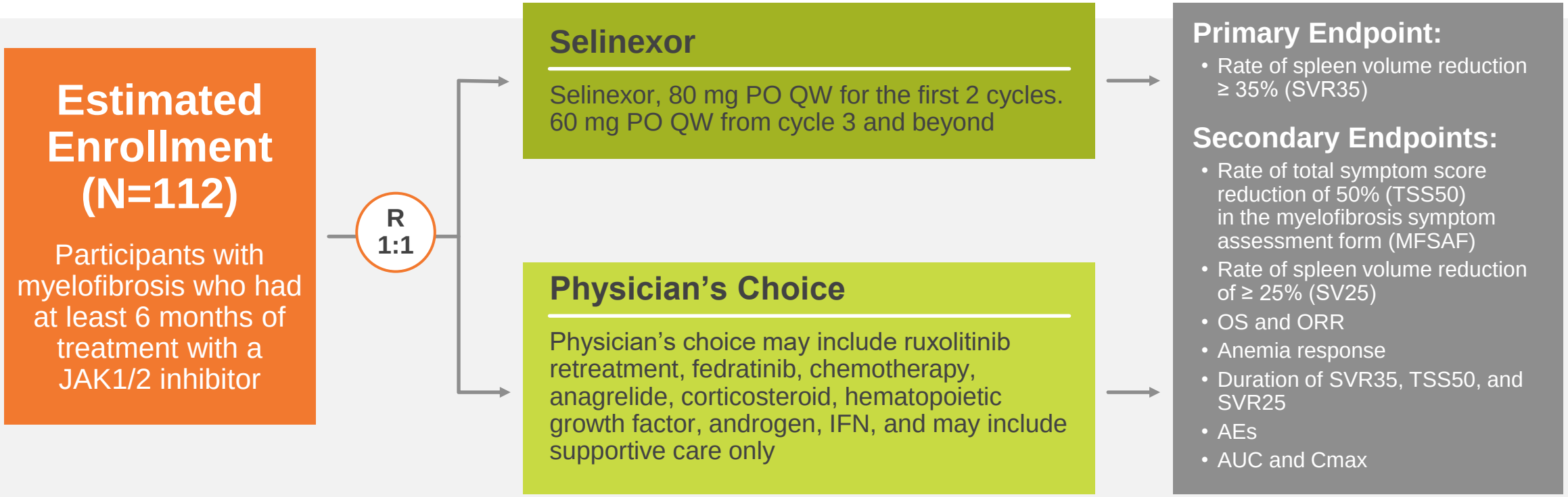
1. Tantravahi, et al. ASH 202 2. Data cut-off as of November 2021
2. Preliminary data cut from investigator sponsored open label trial

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



Top-line data expected in 2H 2023

1. NCT04562870

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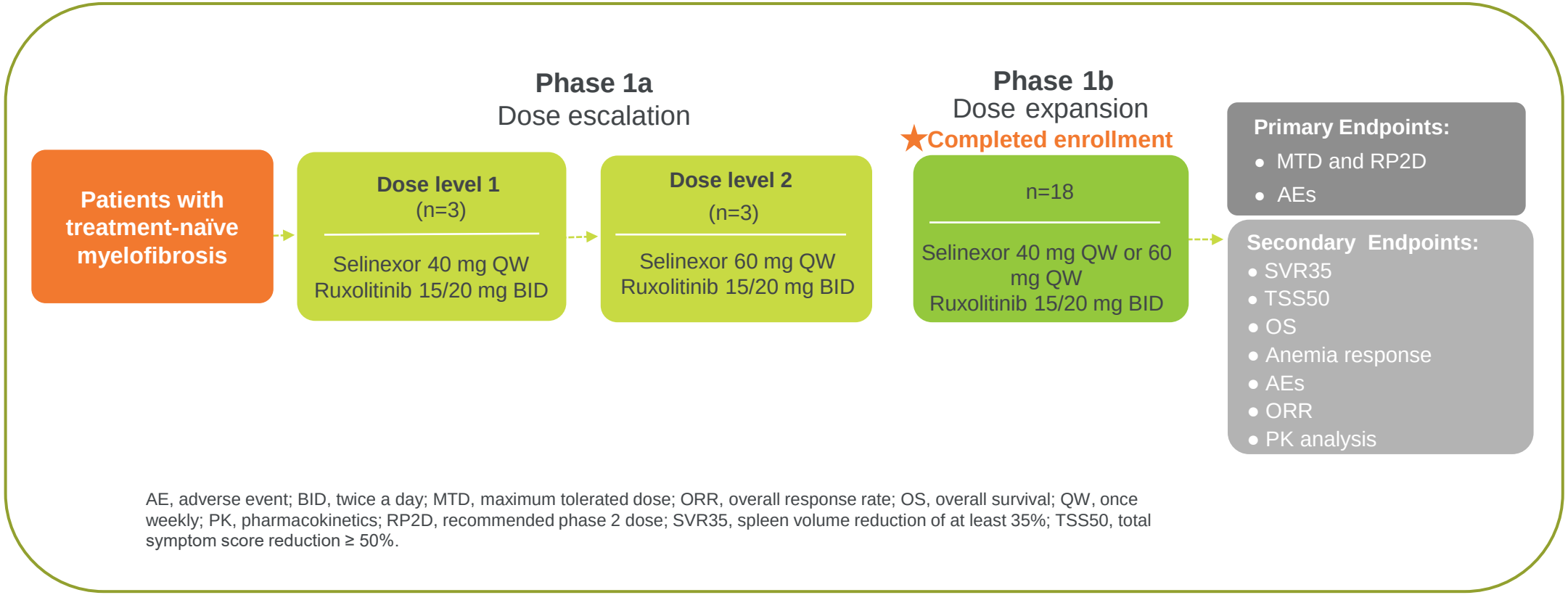
AEs, adverse events; AUC, area under the curve; Cmax, maximum concentration; ; IFN, interferon; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; QW, once weekly

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



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

1. NCT04562389

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Encouraging Preliminary Data[1,2] Across Key Efficacy Endpoints from Phase 1 Study (XPORT-MF-034); Updated Results To Be Presented at ASH 2022

SPLEEN RESPONSES AT 12 & 24 WEEKS

79% of evaluable patients[3] (11/14) achieved SVR35 at week 12

86% of evaluable patients[3] (6/7) achieved SVR35 at week 24

RAPID REDUCTION IN TOTAL SYMPTOM SCORES (TSS)

69% of evaluable patients[3] (9/13) achieved TSS50[4] at week 12

POSITIVE IMPACTS ON HEMOGLOBIN LEVELS

65% of patients[5] (11/17) maintained stable hemoglobin (± 2g/dL) or improved hemoglobin level (>2g/dL increase) at last follow up

SAFETY AND TOLERABILITY

Most common TEAEs[6] (n=19):
Nausea (58%), anemia (42%), vomiting (42%), majority Grade 1-2.
Most common Grade ≥ 3 TEAEs:
Thrombocytopenia (26%) and anemia (21%)

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.

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1. Data cut from July 2022 2. ASH Abstract 2022 3. Efficacy evaluable at 12W: Patients who had a baseline efficacy evaluation and an on-treatment evaluation at 12 weeks; Efficacy evaluable at 24W: Patients who had a baseline efficacy evaluation and an on-treatment evaluation at 24 weeks. 4. TSS50 24W data not available at the time of data submission to ASH 5. Data from 17 transfusion independent patients who had at least 8 weeks of treatment; one patient was transfusion dependent at baseline and not included in the denominator 6. Treatment emergent adverse events

Evolution of Data from Phase 1 Study (XPORT-MF-034) of Selinexor Plus Ruxolitinib in Patients with Treatment-Naïve Myelofibrosis

ASCO 2022
(Poster)

Number of Patients	SVR35@12wks*	SVR35@24wks*
N=15 • n =12 on 60mg • n = 3 on 40mg	75% (6/8)	Not Reported
Most common Gr 3/4 TEAEs**	**TSS50@12wks***	**Stable or Improved Hemoglobin**
Thrombocytopenia and anemia with one Grade 4 TEAEs	43% (3/7)	50% (5/10)

Data Cut = May 2022

ASH 2022
(Abstract)

Number of Patients	SVR35@12wks*	SVR35@24wks*
N=19 • n =15 on 60mg • n = 4 on 40mg	79% ↑ (11/14)	86% (6/7)
Most common Gr 3/4 TEAEs**	**TSS50@12wks***	**Stable / Improved Hemoglobin**
Thrombocytopenia and anemia with two Grade 4 TEAEs	69% ↑ (9/13)	65% (11/17)

Data Cut = July 2022

*Efficacy population: efficacy evaluable patients who received at least one dose of study treatment and one evaluation
**Safety population: patients who received at least one dose of study treatment

- **Presenting Author:** Dr. Haris Ali, City of Hope
- **Session Name:** 634. Myeloproliferative Syndromes: Clinical & Epidemiological: Poster I
- **Session Date:** Saturday, December 10, 2022
- **Presentation Time:** 5:30 PM - 7:30 PM
- **Location:** Ernest N. Morial Convention Center, Hall D

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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

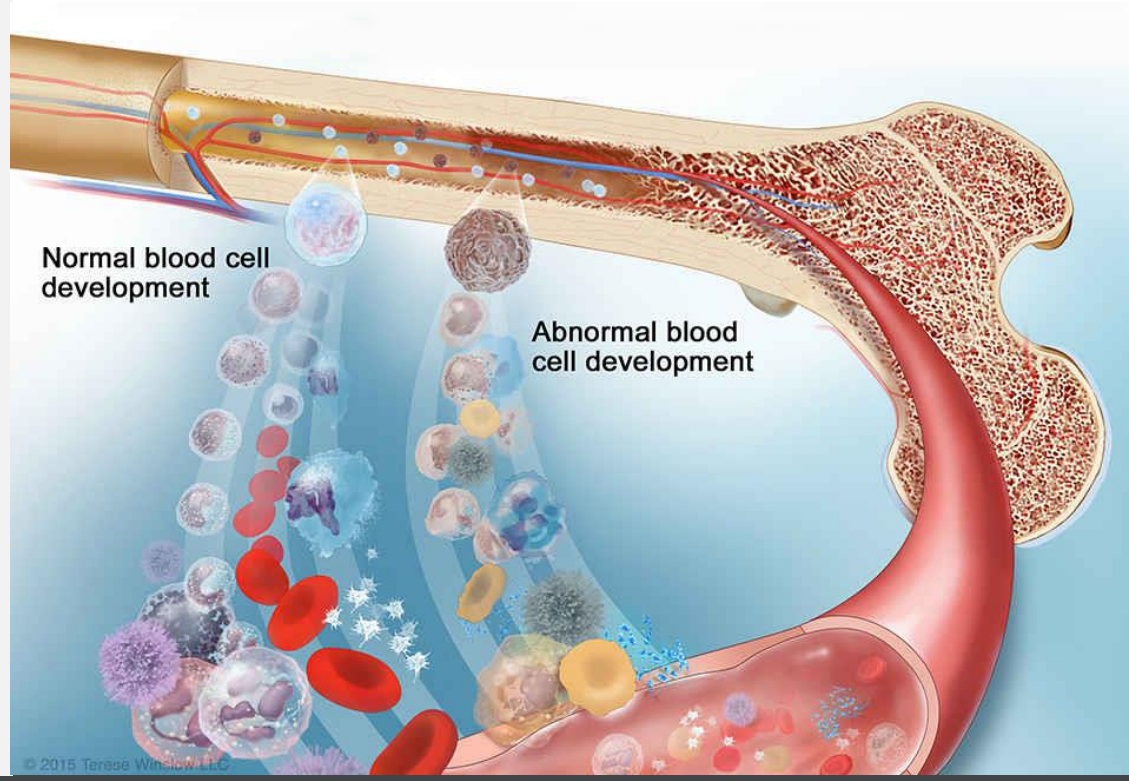
Treatment Landscape

- 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]



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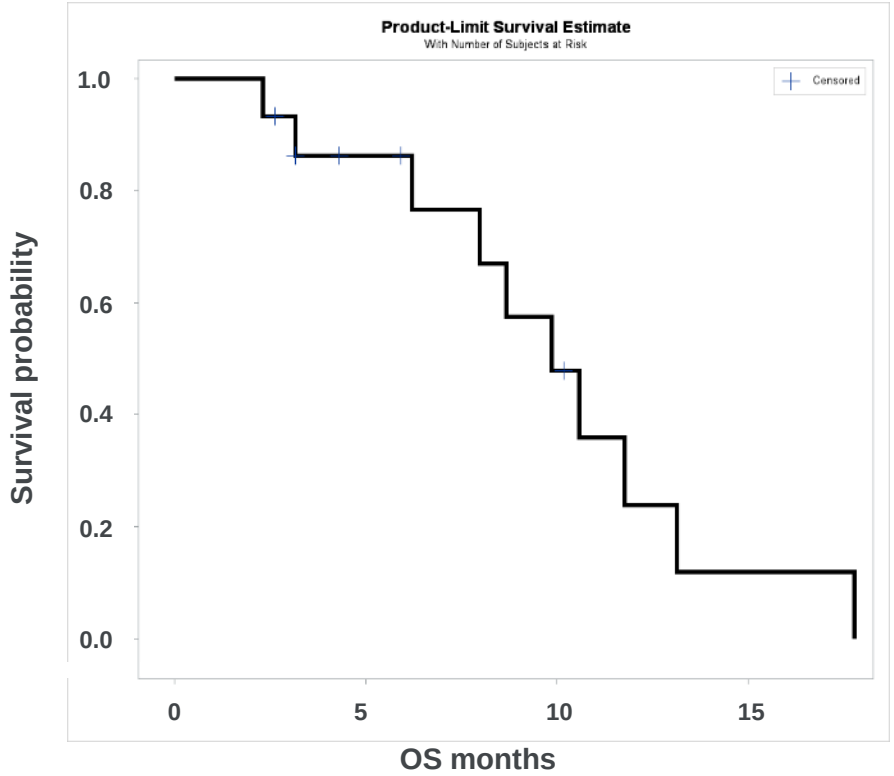
1. Clarivate/DRG Myelodysplastic-Syndrome-Epidemiology-Dashboard (2022 figures, pub 2020) **2.** Gil-Perez A. Ther Adv Hematol. 2019 doi:10.1177/2040620719847059.. **3.** Jabbour E, Cancer. 2010;116(16):3830-4. **4.** Prébet T. J Clin Oncol. 2011;29:3322-7.

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.

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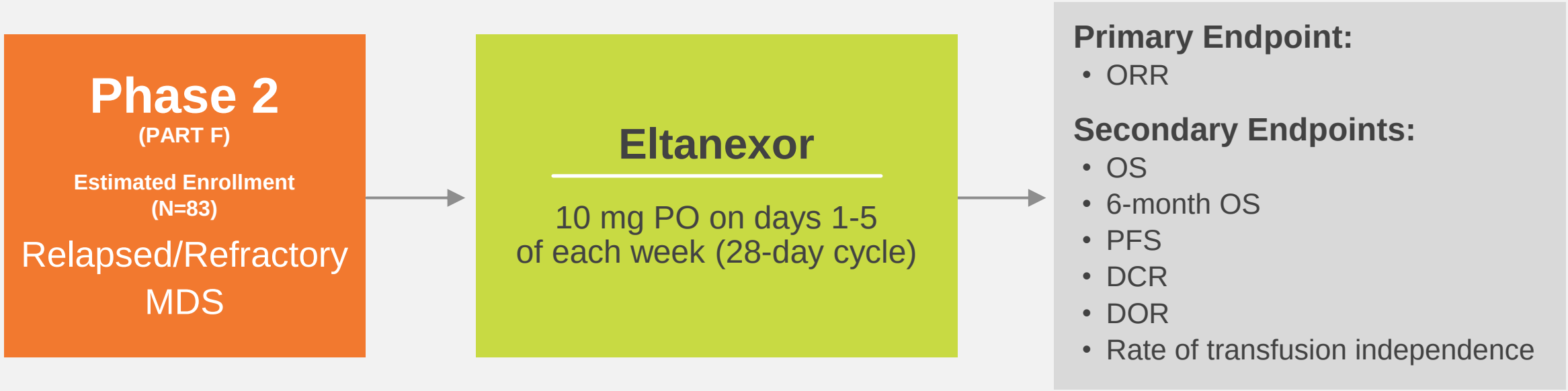
Phase 2 Expansion of the Ongoing Phase 1/2 Study of Single-Agent Eltanexor in Relapsed/Refractory MDS



Data from interim analysis expected in Q4 2022 / Q1 2023

Top-line data expected 2023

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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.

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

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3Q 2022 Financial Results

Statements of Operations (millions)	3Q 2022	3Q 2021
Total Revenue	**$36.1**	**$37.7**
XPOVIO Net Product Revenue	32.0	26.7
License and Other Revenue	4.1	11.0
Total Operating Expenses[1]	**$67.0**	**$81.5**
Cost of Sales	1.0	0.6
Research and Development Expenses	31.4	45.8
Selling, General & Administrative Expenses	34.6	35.1
Net Loss	**$36.3**	**$51.8**
Net Loss per share	**$(0.45)**	**$(0.69)**

Balance Sheet (millions)	September 30, 2022	Dec 31, 2021
Cash, Cash Equivalents, Restricted Cash and Investments	**$150.1**	**$235.6**

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]
  - Cost reduction initiatives aligned with prioritization of core programs reflected in R&D expenses in 2H 2022
- Cash runway expected to be sufficient to fund planned operations into early 2024

1. Total stock-based compensation expense $6.8million in 3Q 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 expenses

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Upcoming Milestones for 2022 and Beyond

- Leverage commercial capabilities and increase U.S. 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 *TP53* 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 (4Q 2022 / 1Q 2023) and top-line data (2023)

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Karyopharm® Therapeutics

Thank you!