Karyopharm® Therapeutics

Virtual Investor Day

December 8, 2021

Forward-looking Statements and Other Important Information

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Karyopharm's guidance on its expected cash runway and 2022 revenue and research and development expenses; expectations and plans relating to XPOVIO or any of its drug candidates, if approved, 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 its drug candidates, if approved, and the commercial performance of XPOVIO; submissions to, and the review and potential approval of selinexor or any of its other drug candidates 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 and eltanexor. Such statements are subject to numerous important factors, risks and uncertainties, many of which are beyond Karyopharm's control, that may cause actual events or results to differ materially from Karyopharm's current expectations. For example, there can be no guarantee that Karyopharm will successfully commercialize XPOVIO; that regulators will grant confirmatory approval in the European Union based on the BOSTON study in adult patients with multiple myeloma; or that any of Karyopharm's drug candidates, including selinexor and eltanexor, will successfully complete necessary clinical development phases or that development of any of Karyopharm's drug candidates will continue. Further, there can be no guarantee that any positive developments in the development or commercialization of Karyopharm's drug candidate portfolio will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this presentation 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 drug candidates, delaying ongoing or planned clinical trials, impeding the execution of business plans, planned regulatory milestones and timelines, or inconveniencing patients; the adoption of XPOVIO in the commercial marketplace, the timing and costs involved in commercializing XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; the ability to obtain and retain regulatory approval of XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; Karyopharm's results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. Food and Drug Administration and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, including with respect to the need for additional clinical studies; the ability of Karyopharm or its third party collaborators or successors in interest to fully perform their respective obligations under the applicable agreement and the potential future financial implications of such agreement; Karyopharm's ability to enroll patients in its clinical trials; unplanned cash requirements and expenditures; development or regulatory approval of drug candidates by Karyopharm's competitors for products or product candidates in which Karyopharm is currently commercializing or developing; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any of its products or product candidates. These and other risks are described under the caption "Risk Factors" in Karyopharm's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, which was filed with the Securities and Exchange Commission (SEC) on November 3, 2021, and in other filings that Karyopharm may make with the SEC in the future. Any forward-looking statements contained in this presentation speak only as of the date hereof, and, except as required by law, Karyopharm expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. Karyopharm regularly uses its website to post information regarding its business, drug development programs and governance. Karyopharm encourages investors to use www.karyopharm.com, particularly the information in the section entitled "Investors," as a source of information about Karyopharm. 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WELCOME, STRATEGIC IMPERATIVES AND CORPORATE VISION

Richard Paulson,
President and Chief Executive Officer

Sharon Shacham, *Co-Founder and Chief Scientific Officer*

Key Opinion Leader Guest Speakers

RAFAEL FONSECA, MD

Getz Family Professor of Cancer

Chair of the Department of Internal Medicine, Director for Innovation and Transformational Relationships, Mayo Clinic Comprehensive Cancer Center

CRISTINA GASPARETTO, MD

Duke University Medical Center

Associate Professor of Medicine, Cellular Therapy Specialist, Hematologic Oncologist, Stem Cell Transplant Specialist

ROBERT COLEMAN, MD, FACOG, FACS

Texas Oncology
US Oncology Research

Chief Scientific Officer

VICKY MAKKER, MD

Memorial Sloan Kettering Cancer Center

Medical Oncologist

GUILLERMO GARCIA-MANERO, MD

MD Anderson Cancer Center

Leukemia physician, Professor of Medicine and Chief of Section of Myelodysplastic Syndromes

SRINIVAS TANTRAVAHI, MBBS, MRCP

University of Utah

Hematology, Internal Medicine and Hematology/Oncology

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Karyopharm Management Team

RICHARD PAULSON, MBA

President and Chief Executive Officer

SHARON SHACHAM, PhD, MBA

Co-Founder, Chief Scientific Officer

JATIN SHAH, MD

Executive Vice President, Chief Medical Officer

SOHANYA CHENG, MBA

Senior Vice President of Sales and Commercial Operations

STEPHEN MITCHENER, PharmD

Chief Business Officer

MICHAEL MASON, MBA, CPA

Chief Financial Officer

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Agenda

Welcome, Strategic Imperatives and Corporate Vision	• **Richard Paulson**, *President and Chief Executive Officer,* **Sharon Shacham, PhD**, *Co-Founder, Chief Scientific Officer*
Multiple Myeloma	• **Jatin Shah, MD,** *Chief Medical Officer*, **Rafael Fonseca, MD,** *Mayo Clinic*, **Cristina Gasparetto, MD**, *Duke University,* **Sohanya Cheng**, *SVP, Sales and Commercial Operations* • **Multiple myeloma Q&A**
Endometrial Cancer	• **Jatin Shah, MD**, *Chief Medical Officer,* **Robert Coleman, MD**, *US Oncology Research,* **Vikky Makker, MD**, *Memorial Sloan Kettering,* **Sohanya Cheng**, *SVP, Sales and Commercial Operations* • **Endometrial cancer Q&A**
BREAK	
Pipeline Prioritization	• **Myelodysplastic Syndromes: Jatin Shah, MD**, *Chief Medical Officer,* **Guillermo Garcia Manero, MD**, *MD Anderson,* **Sohanya Cheng**, *SVP, Sales and Commercial Operations* • **Myelodysplastic Syndromes Q&A** • **Myelofibrosis: Jatin Shah, MD**, *Chief Medical Officer,* **Srinivas Tantravahi, MD**, *University of Utah,* **Sohanya Cheng**, *SVP, Sales and Commercial Operations* • **Myelofibrosis Q&A**
Corporate, Partnerships & Financial	• **Stephen Mitchener**, *Chief Business Officer,* **Michael Mason,** *Chief Financial Officer*
Conclusion	• **Final Q&A and Closing Remarks**

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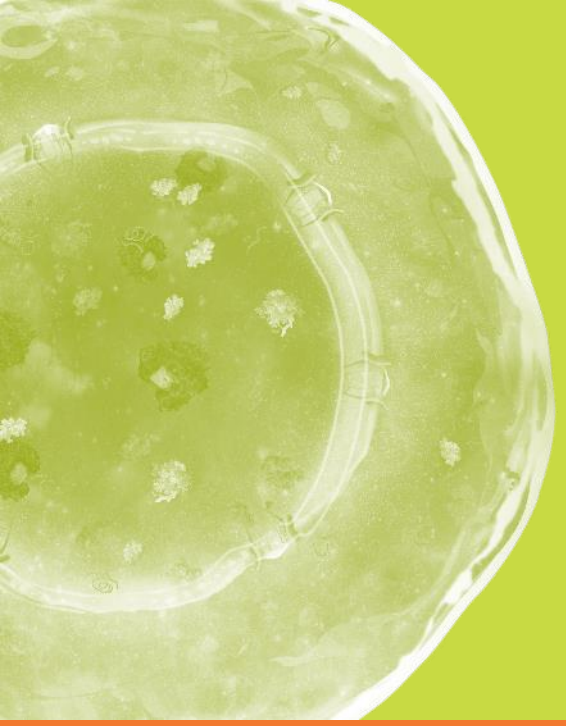

Leveraging the **inhibition of nuclear export** as a mechanism to treat cancer

Karyopharm® Therapeutics

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

Expanding on myeloma foundation

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

Near-term opportunity in solid tumors

SIENDO recruitment complete; top-line Phase 3 results in endometrial cancer in 1Q22

Focused clinical pipeline

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

Strong executive leadership

Ability to achieve commercial and development excellence to execute corporate objectives

Well-capitalized

Cash runway into mid-2023

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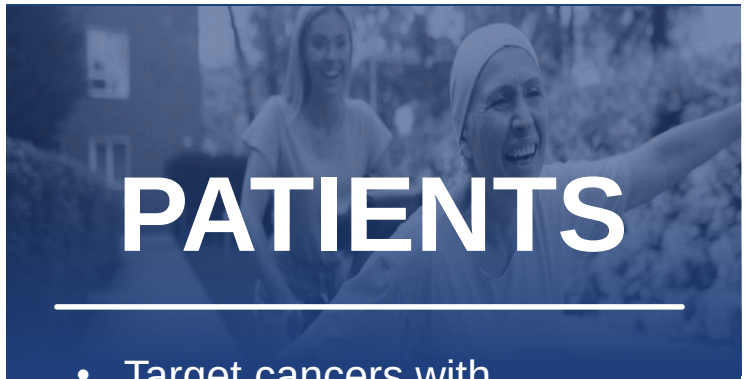
Strategic Imperatives

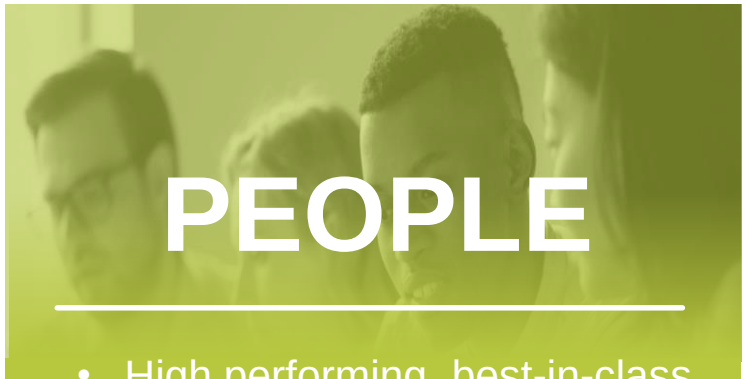


PATIENTS

- Target cancers with high unmet need and high probability of success
- Commercial excellence
- Transform patients' lives

SCIENCE

- Global leader with first-in-class SINE technology
- Approvals in multiple types of hematologic cancer; expansion into solid tumors
- SINE assets with focused pipeline on key indications



PEOPLE

- High performing, best-in-class entrepreneurial culture
- Top talent destination embracing diversity, equity and inclusion
- World class partnerships to maximize global opportunity

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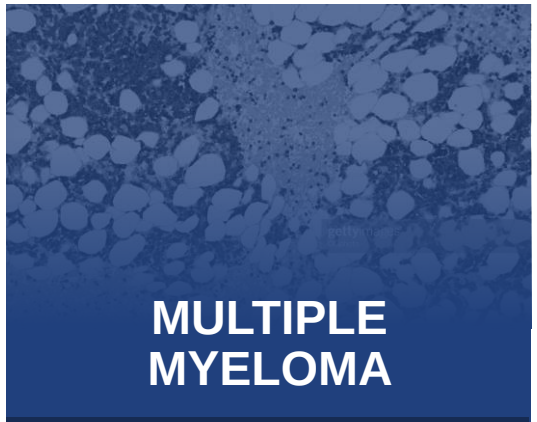
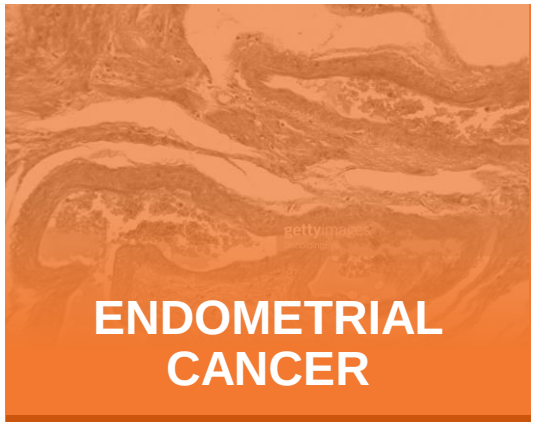
Prioritized and targeted core programs focused on areas of high unmet need driving continued and sustained innovation across our pipeline



MULTIPLE MYELOMA

~40,000 patients (2L+)[1,5]

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



ENDOMETRIAL CANCER

~14,000 frontline patients[2,5]

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

MYELODYSPLASTIC SYNDROMES

~15,000 intermediate to high risk patients[3,5]

Potential to improve survival in HMA-refractory MDS

MYELOFIBROSIS

~5,000 MF patients[4,5]

Potential to improve patient outcomes in JAKi-refractory MF

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

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1. Kantar Cancer Impact. **2.** Sorbe, B et al. Int J Gynecol Cancer 2008. **3.** Clarivate/DRG Epidemiology Data. **4.** https://my.clevelandclinic.org/health/diseases/15672-myelofibrosis. **5.** Annual U.S. incidence.

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	monotherapy	DLBCL (R/R)	XPORT-DLBCL-030[1]				
	monotherapy	Endometrial cancer (maintenance therapy)	SIENDO				
	w/pomalidomide + dexamethasone	Multiple myeloma (2L+)	XPORT-MM-031[2,3,4]				
	w/carfilzomib	Multiple myeloma (relapsed/refractory)	STOMP				
	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 (treatment naive)	KCP-8602-801				

hematologic cancer solid tumor cancer Coming soon

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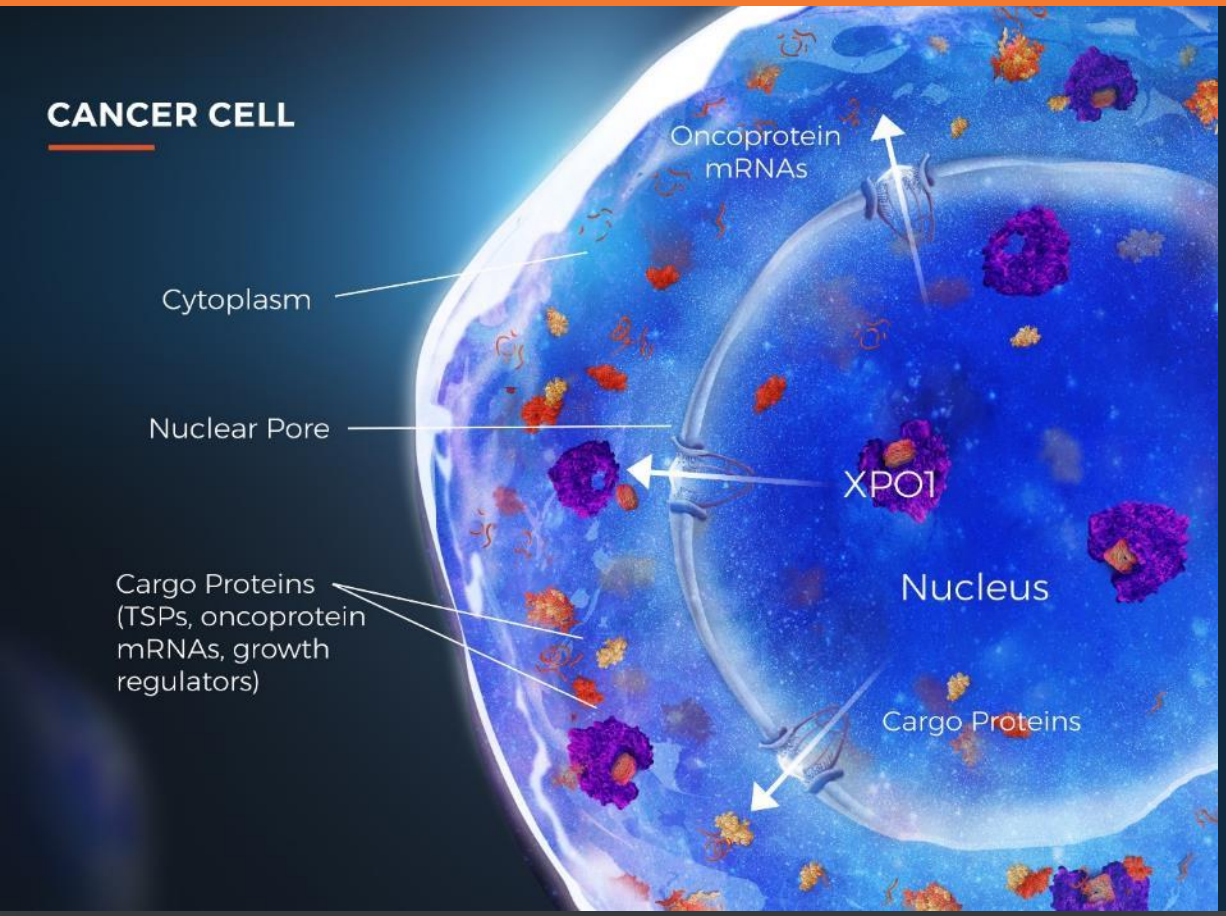
1. XPORT-DLBCL-030 is a Phase 2/3. **2.** Versus elotuzumab, pomalidomide, and dexamethasone. **3.** Study expected to dose first patient in 1Q22. **4.** Sponsored by European Myeloma Network. **5.** XPORT-MF-034 is a Phase 1/2.

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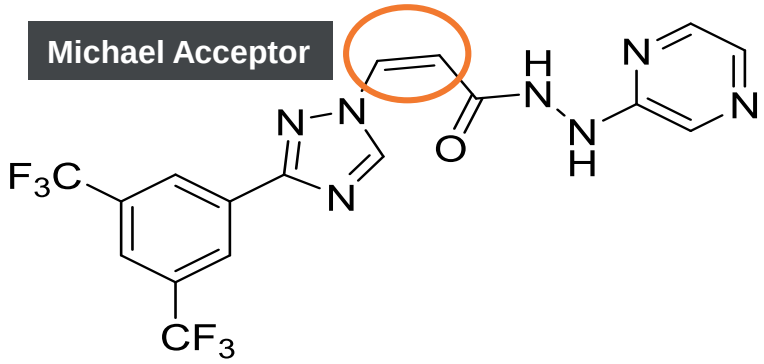
1. Gupta A, et al. J Thorac Oncol. 2017. **2.** Sun Q, et al. Signal Transduct Target Ther. 2016.
3. Gandhi UH, et al. Clin Lymphoma Myeloma Leuk. 2018. **4.** Gravina GL, et al. J Hematol Oncol. 2014

Two Differentiated, Complementary Novel SINE Compounds

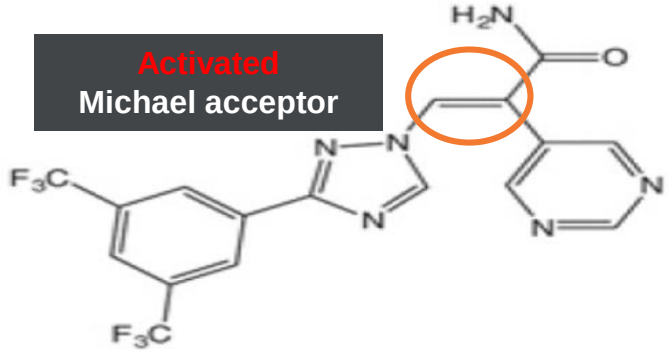
SELINEXOR



- ✓ Only approved, first-in-class SINE compound which leverages once or twice a week dosing
- ✓ FDA approved in MM and DLBCL, with completed recruitment in Ph 3 Endometrial Study
- ✓ Future development builds upon strong foundation to date with programs in both Solid Tumor and Hematology
- ✓ Strong rationale for combinations with I/O agents

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

ELTANEXOR



- ✓ Composition inclusive of an Activated Michael Acceptor
- ✓ 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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MULTIPLE MYELOMA

Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
SVP, Sales and Commercial Operations

Rafael Fonseca, MD
Professor and Chair of the Department of Internal Medicine, Mayo Clinic

Cristina Gasparetto, MD
Associate Professor of Medicine, Duke University

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

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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

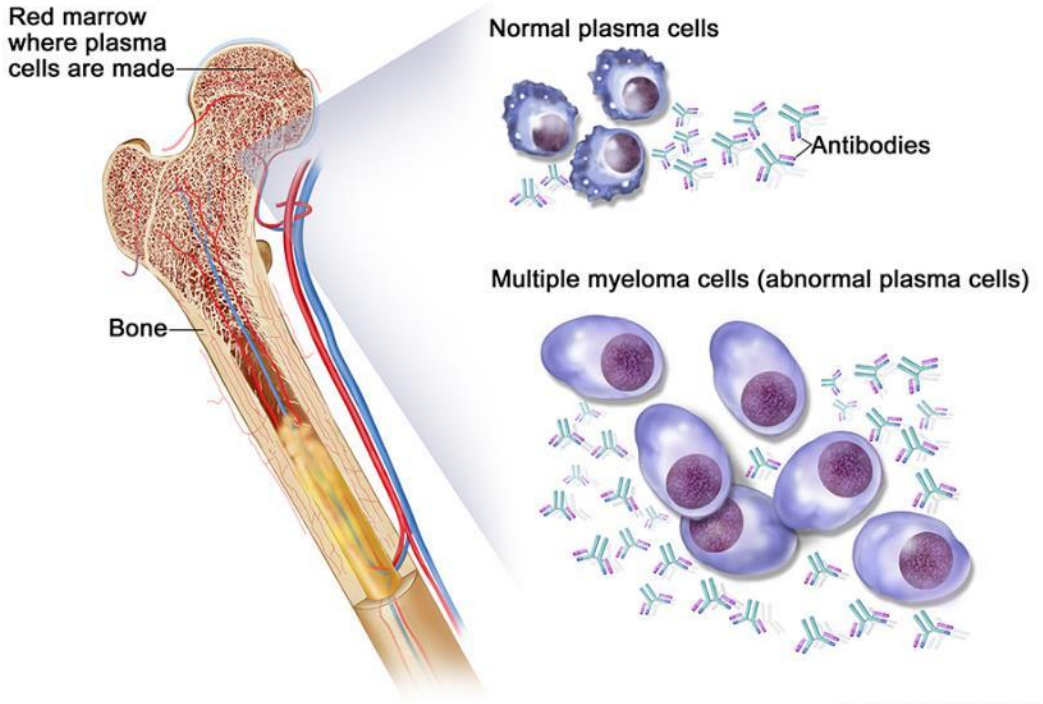
Treatment Landscape

- Following first line progression, **treatment decisions are based on physician 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 who are refractory to prior daratumumab (anti-CD38 mAb)** treatment, including low ORRs and short PFS
- **25%** patients have high-risk cytogenetics and poorer outcomes with currently available therapies[3]

Affects ~40,000 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.** Kantar Cancer Impact. **3.** Am J Hematol. 2020;95:548–567

XPOVIO Dosing has been Refined Over Time to Improve Efficacy and Patient Experience from High Dose BIW to Low Dose QW

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

IN THE BOSTON STUDY

- **65% of patients in the XVd arm had an XPOVIO dose reduction (126/195 patients) vs 35% of those without a dose reduction (69/105)**
- **The median dosage was 80mg (range: 30-137 mg) taken once weekly**
- **Patients had their dosages reduced to mitigate adverse reactions (ARs)**

*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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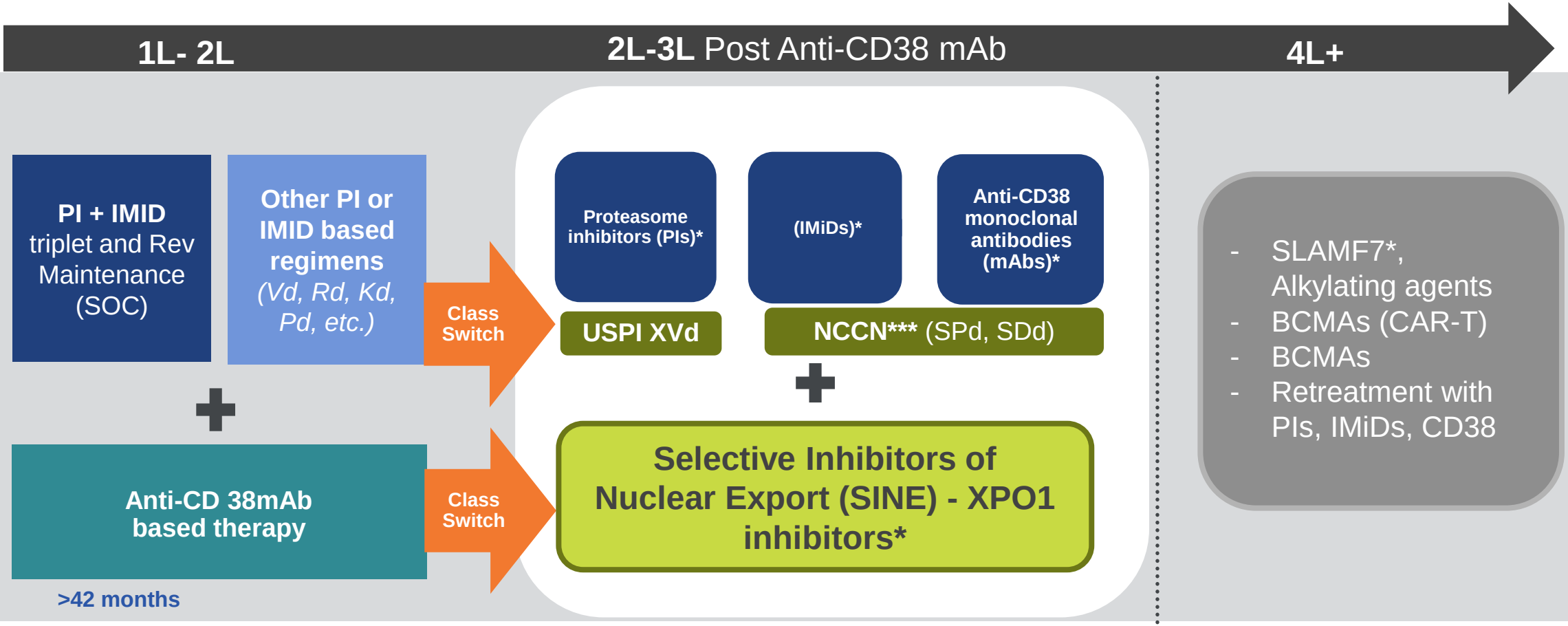
Clarity of Sequencing with XPOVIO-based Regimens Post Anti-CD38mAb in the 2L and 3L Settings of RRMM

XPOVIO provides a mechanistic switch and maintains full optionality to future regimens.



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

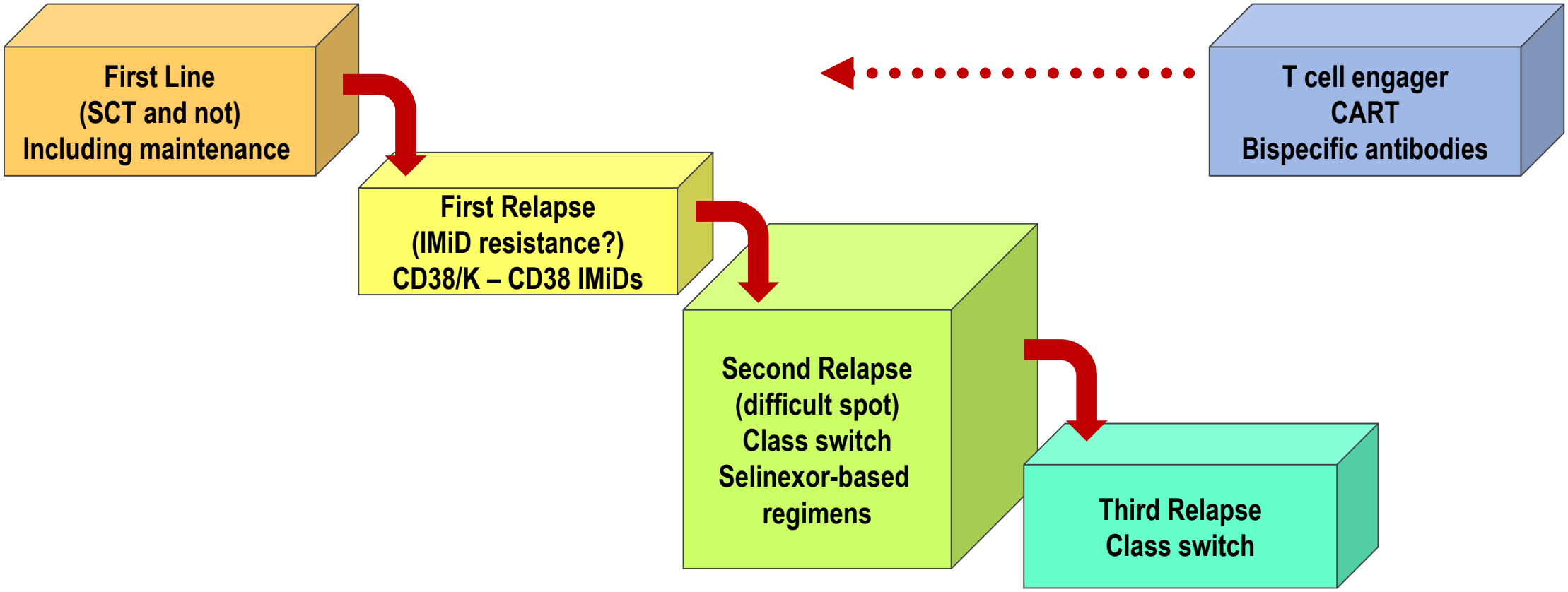
Rafael Fonseca, M.D.
Chief Innovation Officer

Mayo Clinic in Arizona
Multiple Myeloma – Landscape in RR

Phoenix, Arizona

Rochester, Minnesota

Jacksonville, Florida



FRONT LINE	FIRST RELAPSE	SECOND RELAPSE	THIRD RELAPSE
First line	Second line	Third line	Fourth line

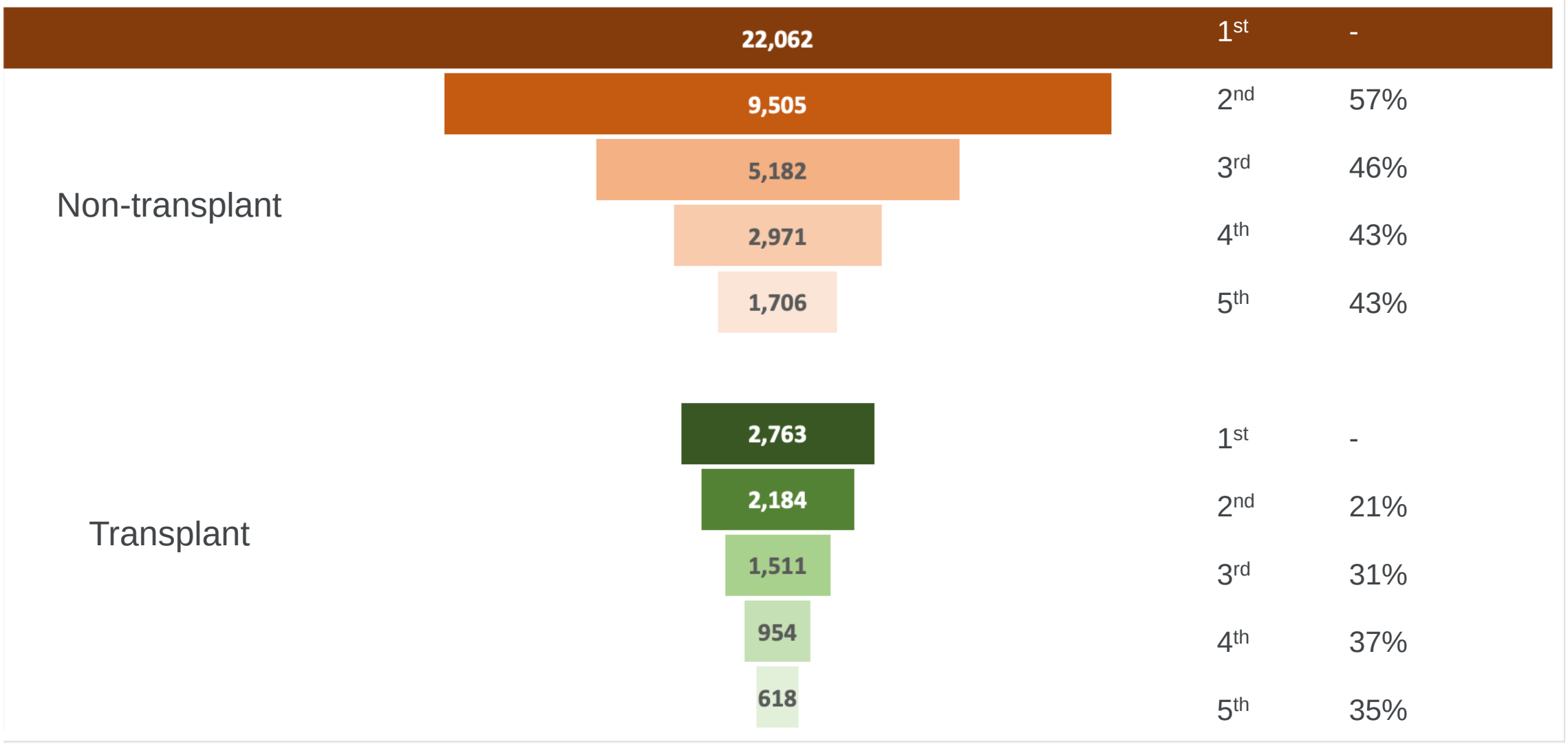
Fonseca, unpublished

Anti-CD38 Increasingly Used for Majority of Patients for First Two Lines with Ongoing Shift to First Line

Studies	POLLUX[1] DRd vs Rd	APOLLO[2] DPd vs Pd	CANDOR[3] DKd vs Kd	MAIA[4] DRd vs Rd	CASTOR[5,6] DVd vs Vd	ICARIA[7] IPd vs Pd	IKEMA[8] IKd vs Kd
	Leukemia 2020	Lancet Onc 2021	Lancet 2020	NEJM 2019	2 publications	Lancet 2019	Lancet 2021
	Daratumumab					Isatuximab	
Eligibility (prior lines of Rx)	1	1-3	1-3	NDMM	1	2+	1-3
n	569	304	466	737	498	307	302
mPFS Exp (mos)	44.5	12.4	28.6	44.5	16.7	11.5	NR
mPFS Control (mos)	17.5	6.9	15.2	17.5	7.1	6.5	19.2
Median # prior lines	1	2	2	0	2	3	2
1 prior line	53%	11%	46%	NA	49%	0	44%
2 prior lines	30%	89% (combined)	54% (combined)	NA	28%	0	36%
3 or more	19%	89% (combined)	54% (combined)	NA	24%	100%	20%
High risk	15%	38%	15%	14%	8%	20%	24%
Deletion 17p13	11%	NA	NA	Not defined	5%	NA	NA
ORR Experimental	93%	69%	84%	93%	85%	60%	87%
MRD Experimental	22%	9%	14%	81%	63%	5% (-5)	30%

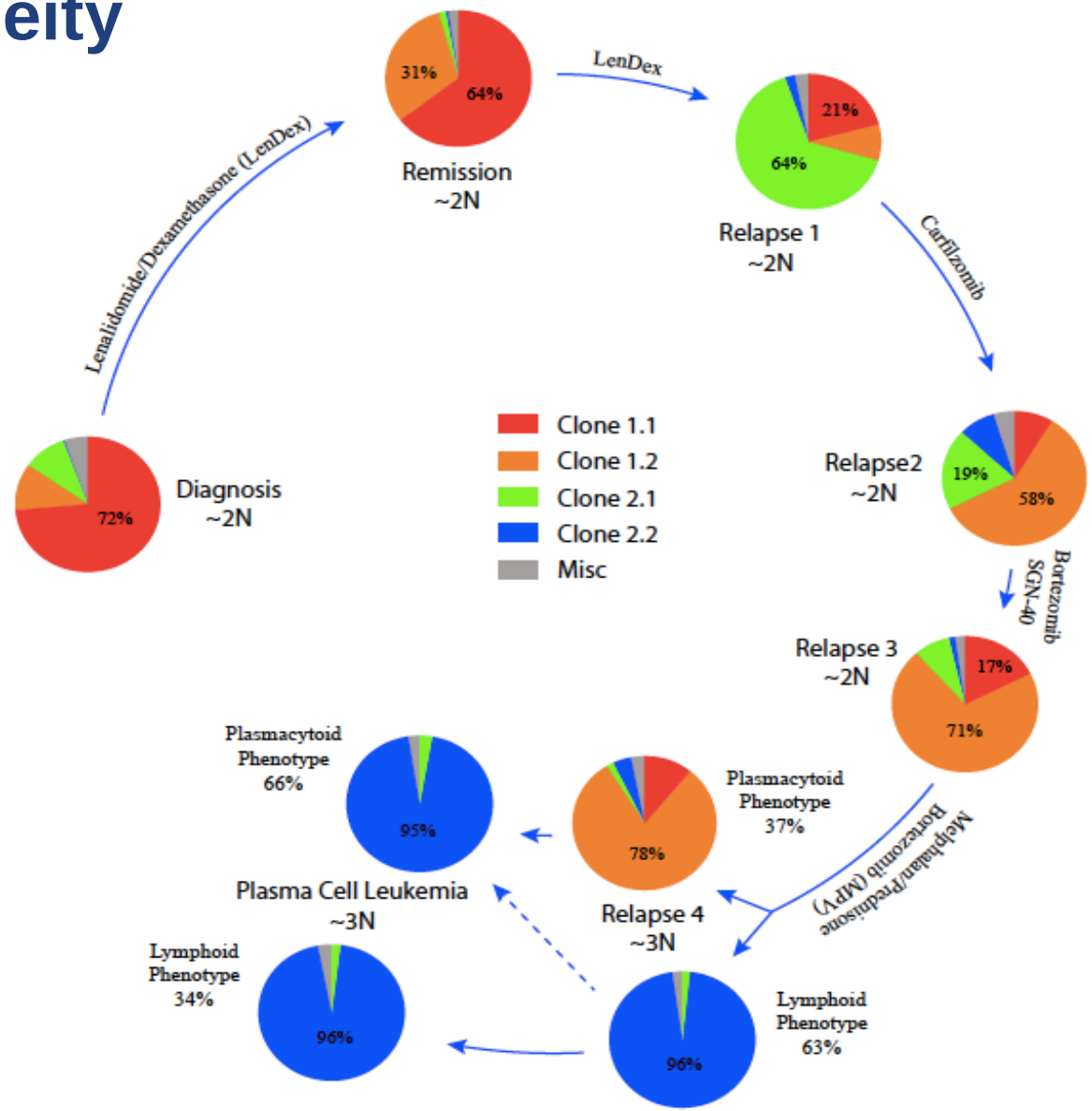
1. Bahlis, et al. Leukemia. 2020 Jul;34(7):1875-1884. **2.** Dimopoulos, et al. Lancet Oncol. 2021 Jun;22(6):801-812. **3.** Dimopoulos, et al. Lancet. 2020 Jul 18;396(10245):186-197. **4.** Facon, et al. N Engl J Med. 2019 May 30;380(22):2104-2115. **5.** Weisel et al. Am J Hematol. 2020 May;95(5):548-567. **6.** Mateos, et al. Clin Lymphoma Myeloma Leuk. 2020 Aug;20(8):509-518. **7.** Attal, et al. Lancet. 2019 Dec 7;394(10214):2096-2107. **8.** Moreau, et al. Lancet. 2021 Jun 19;397(10292):2361-2371.

Attrition with subsequent treatment



Fonseca et al BMC 20: 1087 (2020)

Clonal heterogeneity



Keats et al Blood. 2012 Aug 2; 120(5): 1067–1076

BOSTON Trial: Phase 3 – Vd vs XVd

Randomization 1:1

XVd Weekly 35-day cycles	Selinexor (oral) Bortezomib (SC) Dexamethasone (oral)	100 mg 1.3 mg/m^2 20 mg	Days 1, 8, 15, 22, 29 Days 1, 8, 15, 22 Days 1, 2, 8, 9, 15, 16, 22, 23, 29, 30
Vd Twice Weekly 21-day cycles Cycles 1-8	Bortezomib (SC) Dexamethasone (oral) If IRC confirmed PD: crossover to XVd or Vd permitted	1.3 mg/m^2 20 mg	Days 1, 4, 8, 11 Days 1, 2, 4, 5, 8, 9, 11, 12

Vd Weekly*
35-Day cycles
Cycles ≥9

PD or unacceptable toxicity

Primary endpoint: PFS
Key secondary endpoints:
- ORR
- ≥VGPR
- Grade ≥2 PN

Secondary endpoints:
- OS
- DoR
- TTNT
- Safety

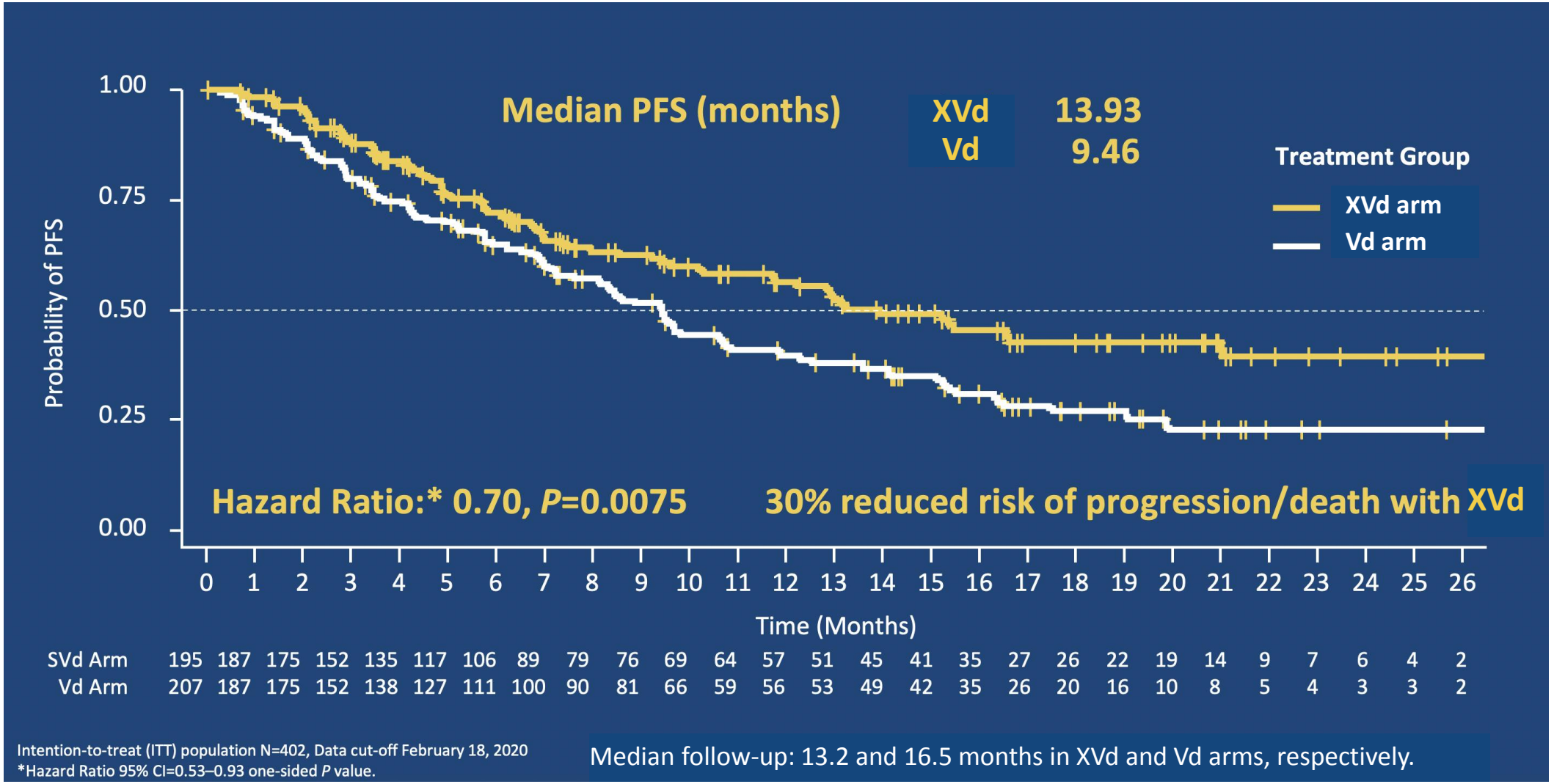
Efficacy Assessed by IRC

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

Stratification: Prior PI therapies (Yes vs No)
Number of prior anti-MM regimens (1 vs >1)
R-ISS stage at study entry (Stage III vs Stage I/II)

5HT-3 prophylactic recommended in XVd arm

BOSTON Trial: PFS



Dose Reduction can be Used to Manage Patients, while Optimizing Outcomes with PFS of 16.6 Months

The median dosage of XPOVIO in the BOSTON trial was 80 mg (range: 30-137 mg) taken once weekly[1]

Key efficacy endpoints for patients (N=195) with and without XPOVIO dose restrictions in the BOSTON trial[2]

	ITT Patient Population	Patients with Dose Reduction
Patient population	N=195	n=126
% of ITT arm	100	65
mPFS, mo	13.9 (95% CI:11.7, NE)	16.6 (95% CI:12.9, NE)
ORR, %	76.4	81.7
≥VGPR, %	44.6	51.6
mDOR, mo	20.3 months (95% CI:12.6, NE)	Not evaluable (95% CI: 13.8, NE)

Limitation of subgroup analyses:

- This post hoc analysis was exploratory in nature, not included in the study objectives, and does not control for type 1 error
- This post hoc analysis was not powered or adjusted for multiplicity to assess PFS across other prespecified subgroups
- This post hoc analysis was underpowered to detect clinically meaningful differences in treatment effect

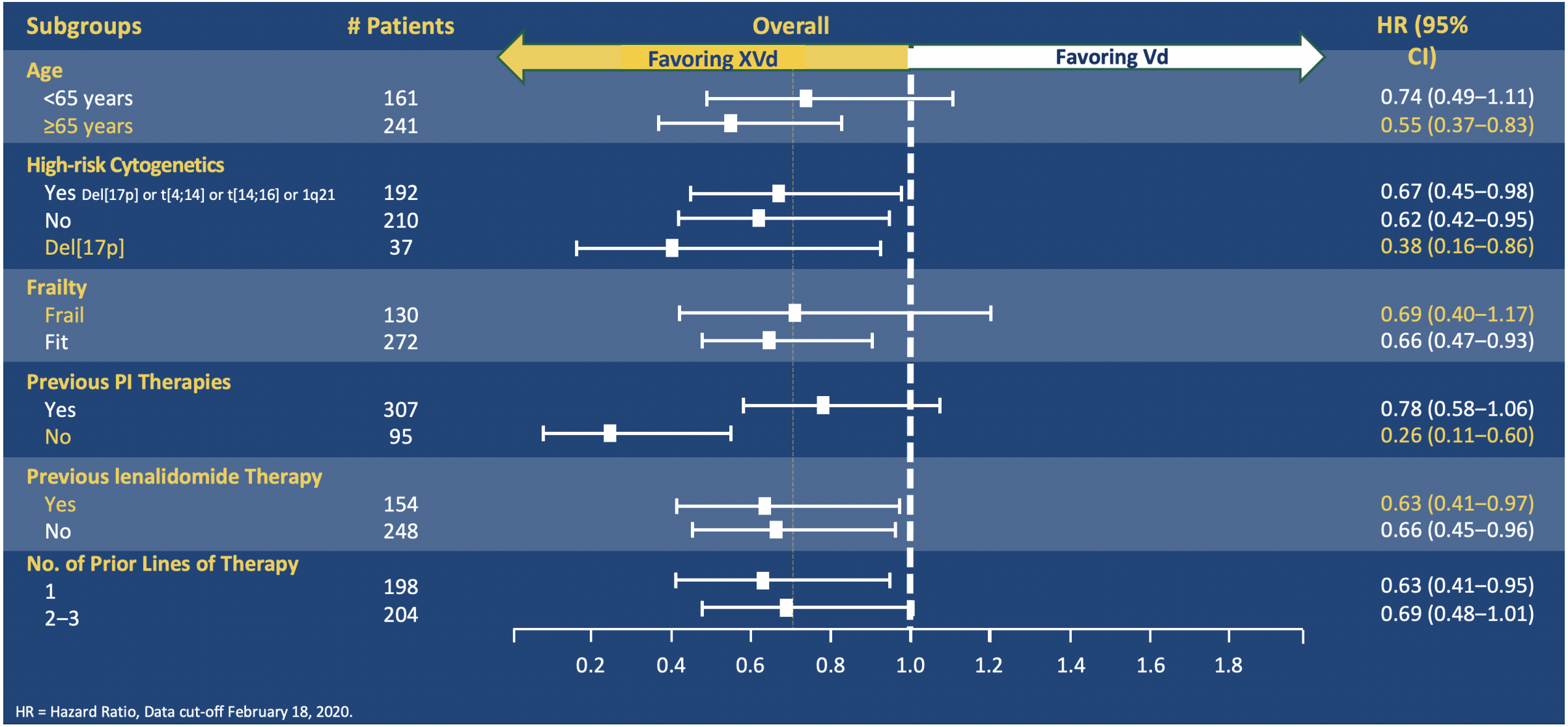
65% of patients in the XVd arm had an XPOVIO dose reduction (126/195 patients) vs 35% of those without a dose reduction (65/195 patients)[2]

*Response was evaluable in 125 of 126 patients receiving a dose modification for selinexor and 66 of the 69 patients who did not receive a dose modification for selinexor. Overall response rate is the proportion of patients who achieve a partial response or better, before IRC-confirmed progressive disease or initiating a new MM treatment or crossover.

CI=confidence interval, IRC=independent review committee; ITT=intent to treat; mDOR=median duration of response; mo=month; mPFS=median progression-free survival; NE=not evaluable; ORR=overall response rate; VGPR=very good partial response.

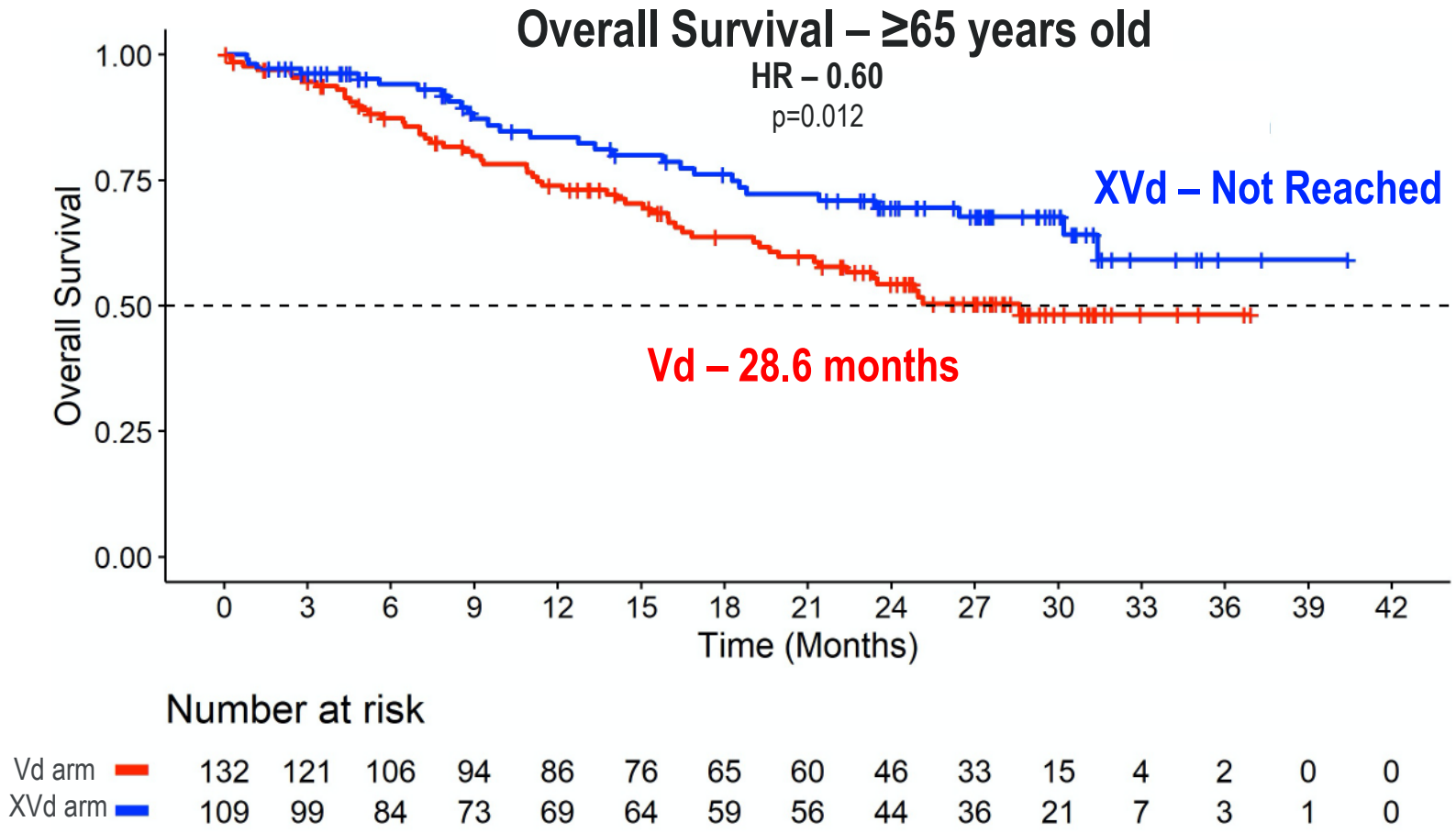
1. XPOVIO. Prescribing information. Karyopharm Therapeutics Inc; 2021. **2.** Jagganath, et al. ASH 2021.

BOSTON Trial: Forest Plot



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

XVd Led to Improved OS in Patients ≥65 year-old[1]



- OS was significantly improved in XVd *vs.* Vd ≥65 year-old patients
- mOS was **not reached** *vs.* **28.6** months (HR, 0.60; 95% CI, 0.38-0.94; p=0.012)
- In <65-year-olds, mPFS was **31.7** months *vs.* **not reached** (HR, 1.51; 95% CI, 0.86-2.68; p=0.926)
- Trend toward OS improvement in all patients on XVd

Facon, et al. ASCO 2021.

New Preclinical Data Supporting Selinexor Treatment in Daratumumab-Refractory MM to be Presented at ASH 2021

Title:	Rationale for Selinexor Treatment in Daratumumab-Refractory MM Patients Identified By Paired Ex Vivo Drug Sensitivity and RNA-seq
Lead author:	Praneeth Reddy Sudalagunta, PhD
Abstract #:	893
Session:	651. Multiple Myeloma and Plasma Cell Dyscrasias: Basic and Translational: Myeloma pathogenesis and novel targets
Date and time:	Monday, December 13, 2021: 7:15 PM

CONCLUSIONS

- *Ex vivo* drug sensitivity data suggests MM patients treated with Daratumumab are more sensitive to selinexor
- Increased MYC expression was identified as a putative predictive biomarker for selinexor sensitivity.
- Clinically validated in STOMP & XPORT-028 trials, which showed deeper response and longer PFS in patients who have received anti-CD38 monoclonal antibody as prior line of therapy
- MM patients could benefit from sequencing selinexor with daratumumab.

Clinical Activity of XPOVIO was Observed in Patients Previously Treated with Daratumumab-containing Regimens[1,2]

The XVd arm of the BOSTON trial showed mPFS of 13.9 months (95% CI: 11.7, NR) compared with 9.5 months (95% CI: 7.6, 10.8) in the Vd arm (N=402)[1]

PFS in patients previously treated with daratumumab in the BOSTON trial (n=17)[2]

12.22 months

mPFS, XVd
(95% CI: 2.86, NR)

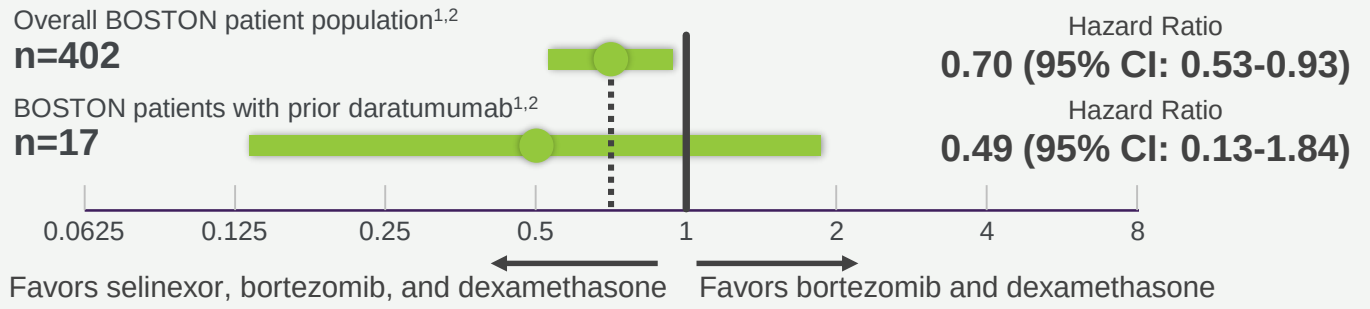
5.55 months

mPFS, Vd
(95% CI: 0.69, NE)

CI=confidence interval; mPFS=median progression-free survival; NE=not evaluable; NR=not reached; ORR=overall response rate; OS=overall survival; PN=peripheral neuropathy; VGPR=very good partial response.

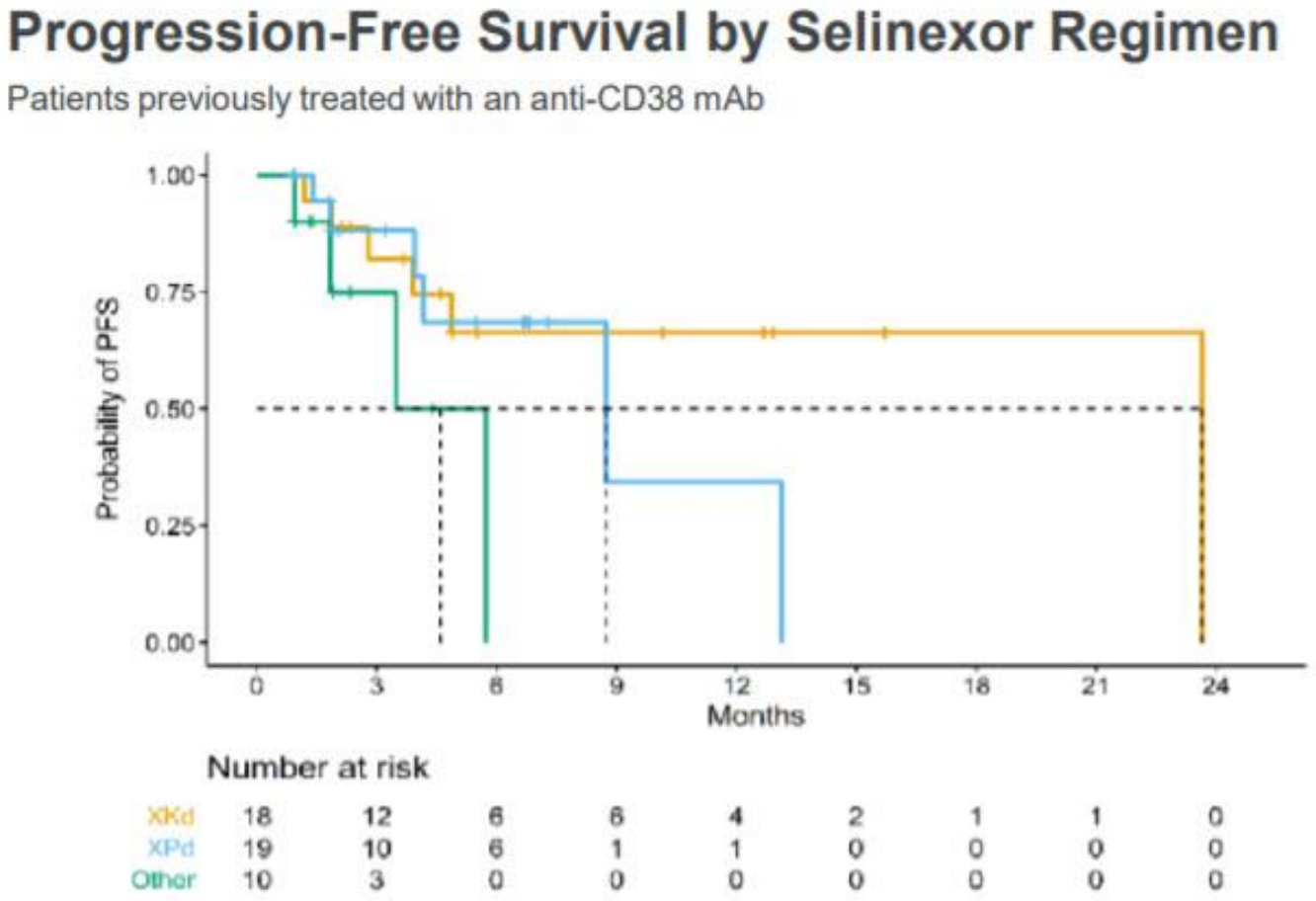
Limitations of subgroup analyses:

- These subgroup analyses were exploratory in nature, not included in the study objectives, and do not control for type 1 error
- These subgroup analyses were not powered or adjusted for multiplicity to assess PFS across this prespecified subgroup
- These subgroup analyses are underpowered to detect clinically meaningful differences in treatment effect



1. XPOVIO. Prescribing information. Karyopharm Therapeutics Inc; 2021. **2.** Grosicki S, et al. *Lancet*. 2020;396(10262):1563-1573.

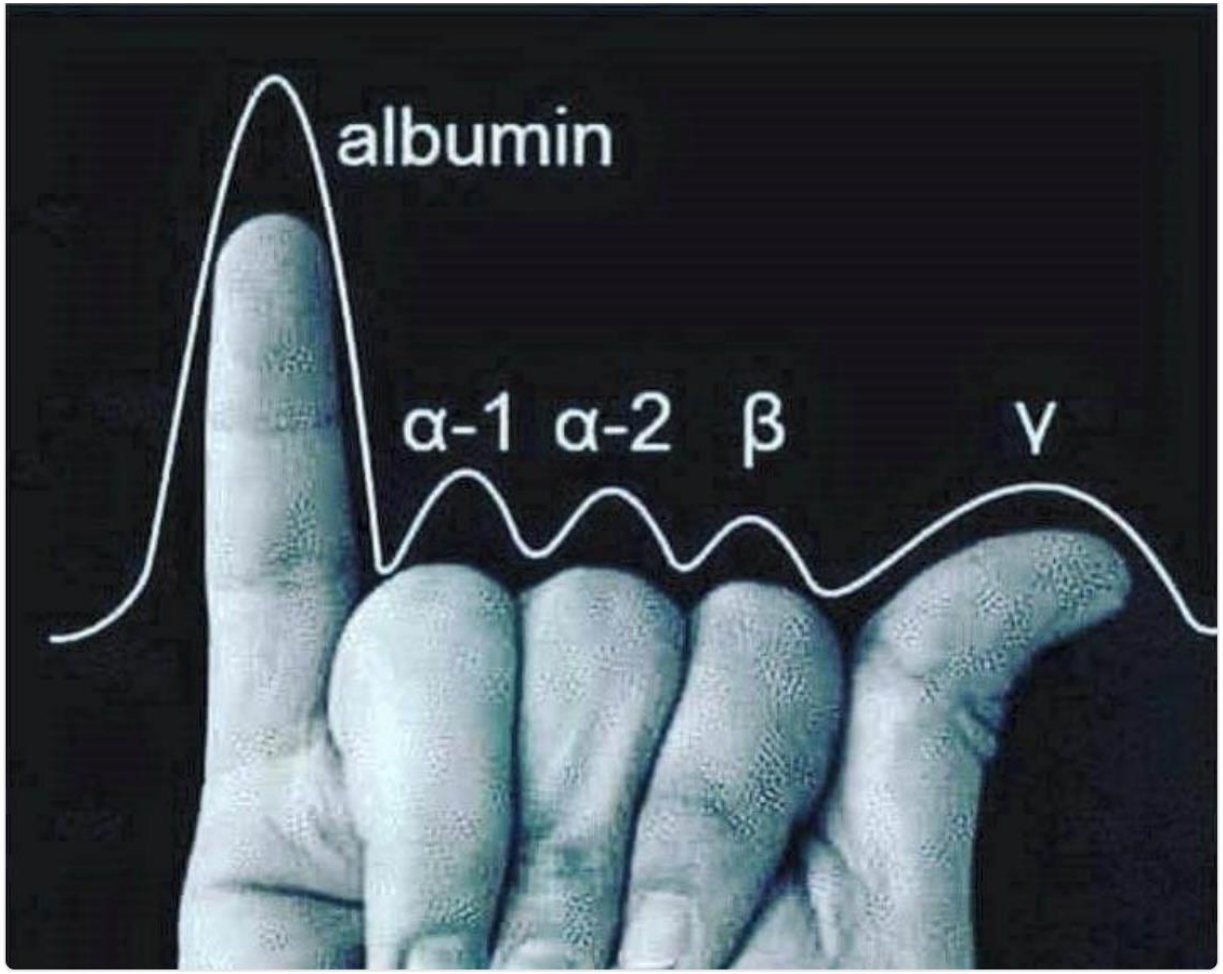
Growing Body of Data Support Use of Selinexor Based Regimens Post-Daratumumab Regimens



- SKd and SPd appear to be very active in the post-daratumumab setting[1]
- Including in patients with high-risk cytogenetics[1]

1. Gasparetto, et al. ASCO 2021.

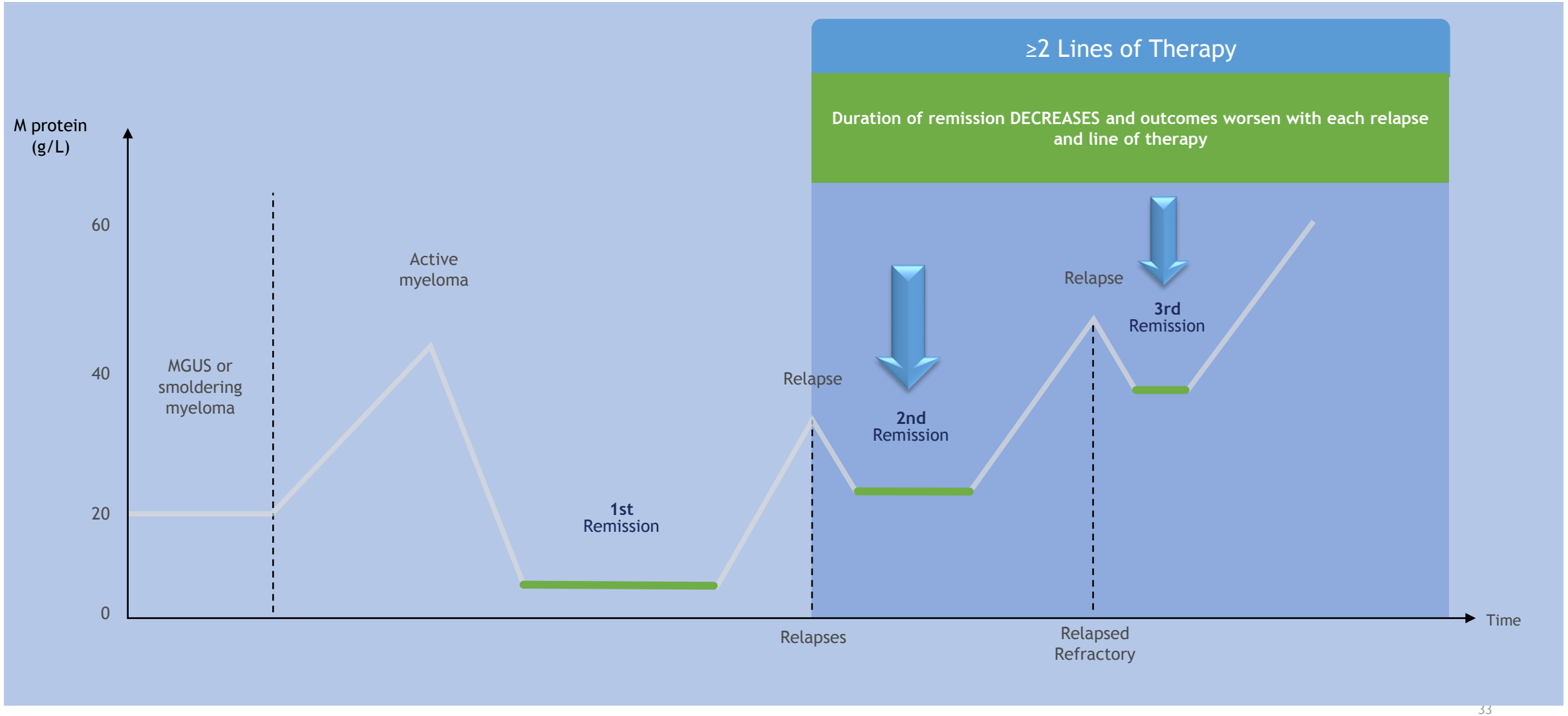
Thank you!



Cristina Gasparetto, MD

Duke University Medical Center

Patients With Multiple Myeloma Will Inevitably Relapse and/or Become Refractory to Certain Treatments

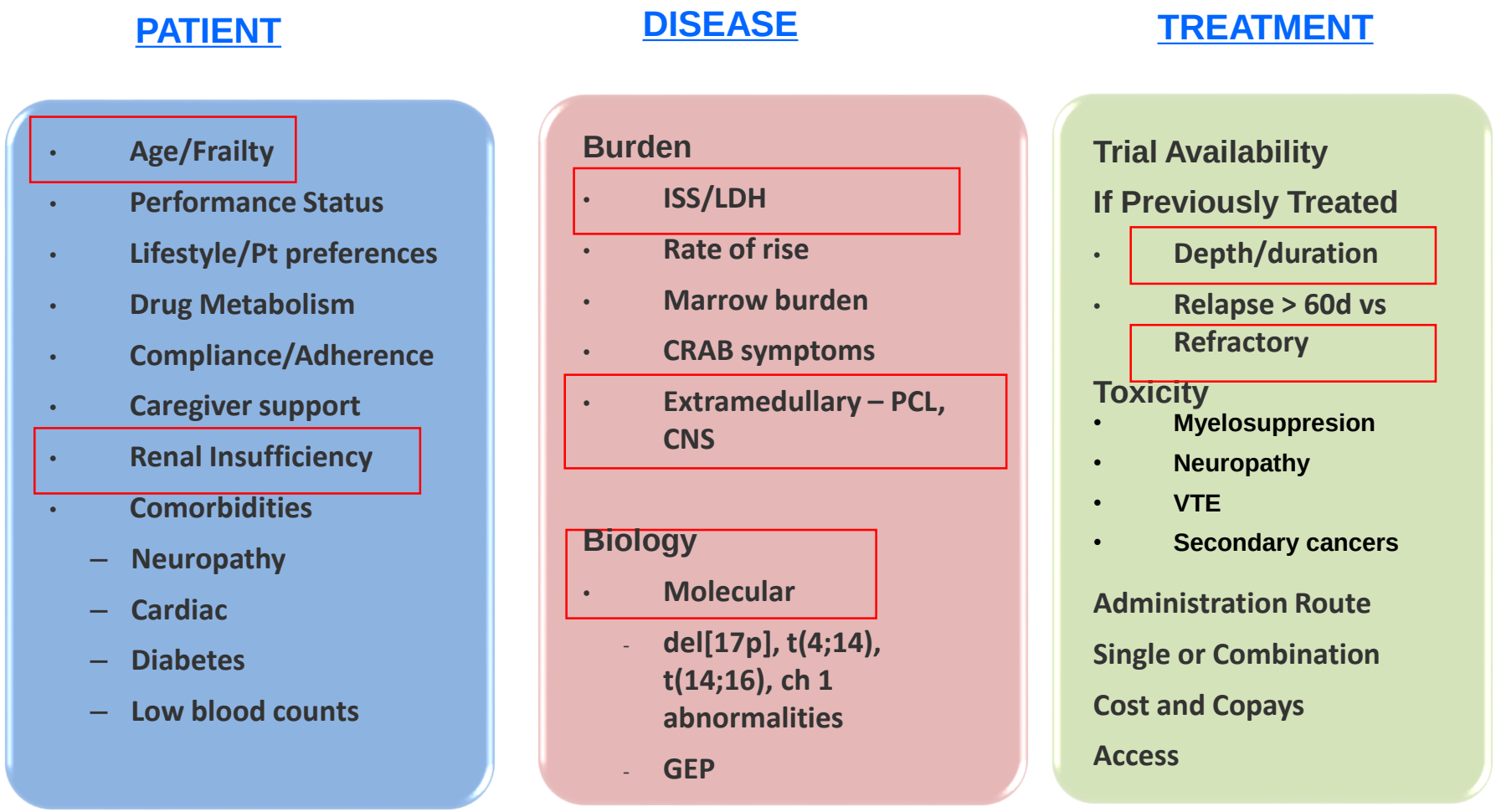


Available Treatments for Multiple Myeloma

Proteasome inhibitors	Immuno-modulator Agents	Monoclonal antibodies	Xportin-1 Inhibitor	Anti-BCMA
• Bortezomib (V) • Carfilzomib (K) • Ixazomib	• Lenalidomide (R) • Pomalidomide (P) • Thalidomide (T)	• Daratumumab (Dara) • Elotuzumab (Elo) • Isatuximab (Isa)	• Selinexor	• Belantamab mafodotin • Ide-cel

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 4.2021).

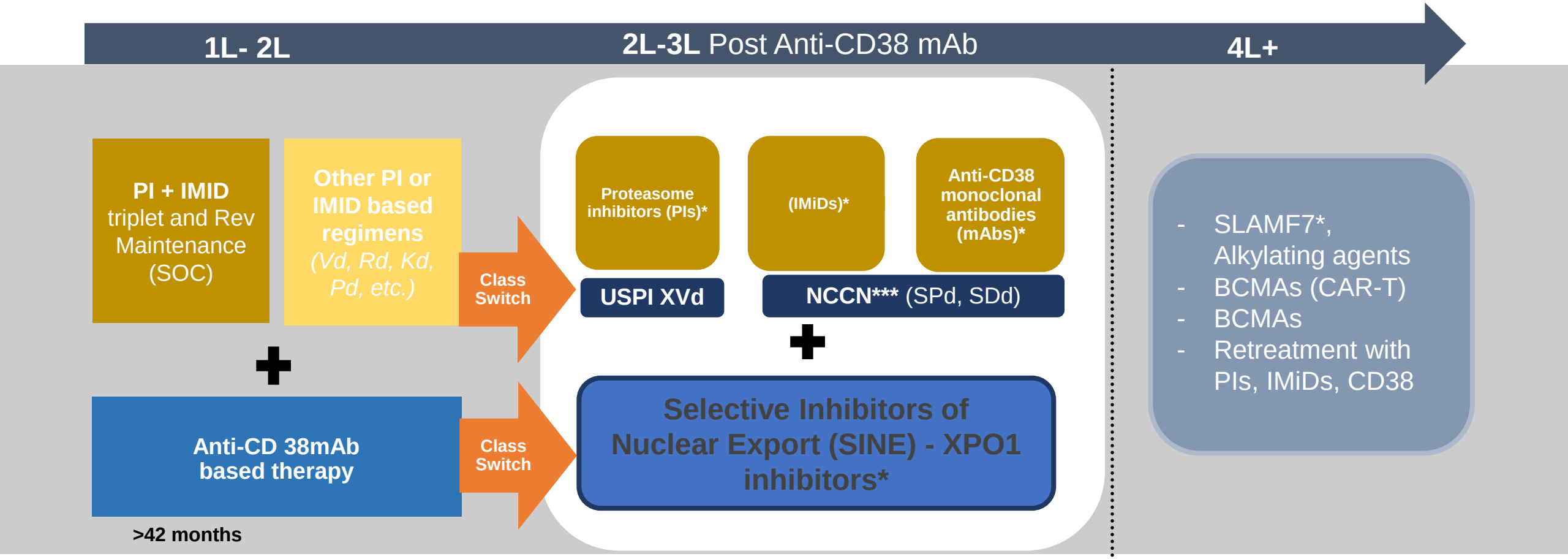
Factors in Selecting MM Therapy and in Outcomes: In 2L+ >80% of Patients Impacted by Multiple Risk Factors[1-4]



1. American Cancer Society: Risk Factors for Multiple Myeloma. https://www.cancer.org/cancer/multiple-myeloma/causes-risks-prevention/risk-factors.html. **2.** Abdallah, et al. Cytogenetic abnormalities in multiple myeloma: association with disease characteristics and treatment response. *Blood Cancer J.* 10, 82 (2020). **3.** Sonneveld, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood* 2016; 127 (24): 2955–2962. **4.** Dimopoulos, et al. Pathogenesis and treatment of renal failure in multiple myeloma. *Leukemia* 22**,** 1485–1493 (2008).

Clarity of Sequencing with XPOVIO-based Regimens Post Anti-CD38mAb in the 2L and 3L Settings of RRMM

XPOVIO provides a mechanistic switch and maintains full optionality to future regimens.

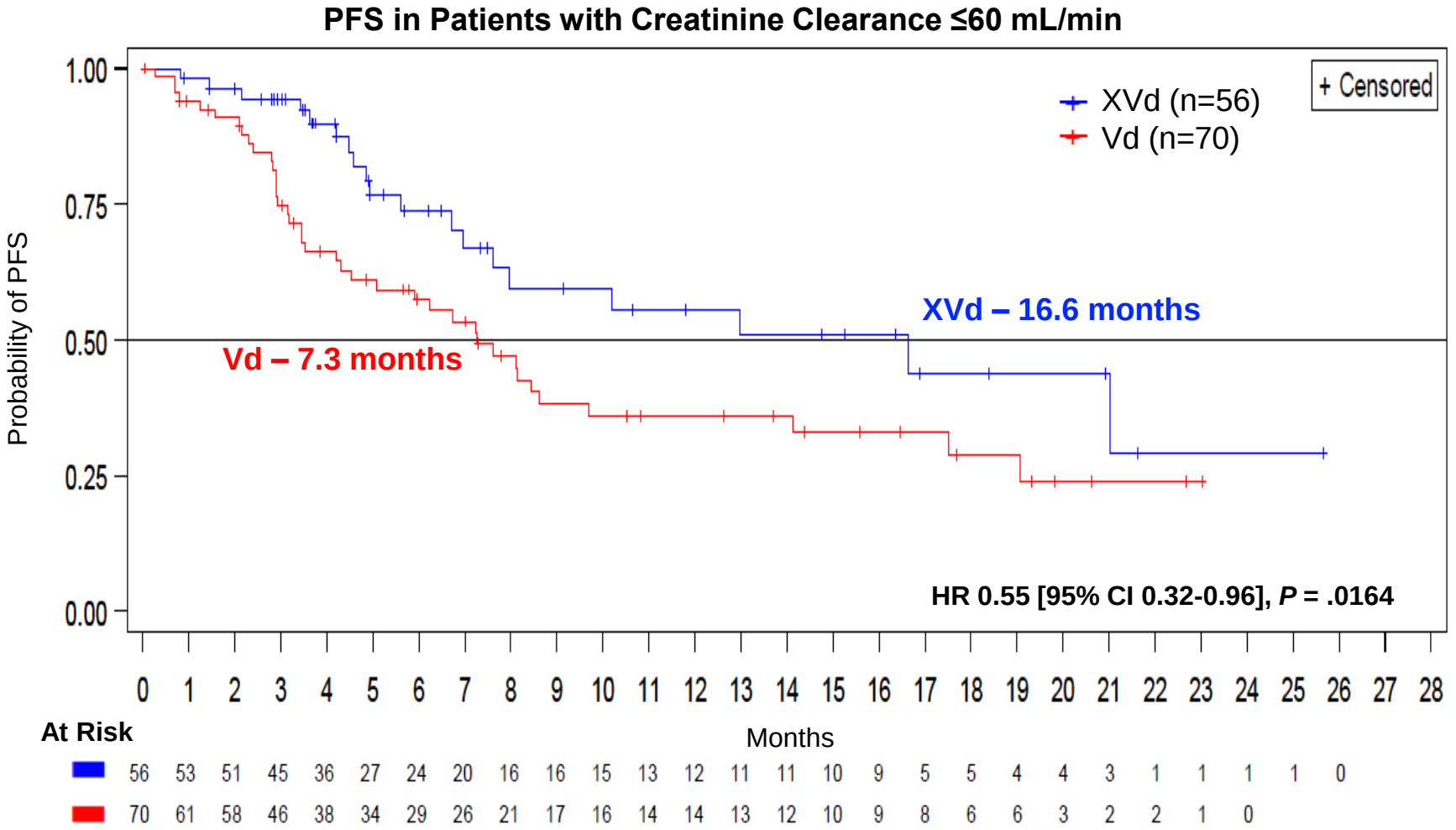


Combinations other than XVd and Xd are not promoted by Karyopharm, but may be considered for future indication updates

* +dexamethasone

*** NCCN Guideline inclusion for SPd and SDd

Data Demonstrated Longer PFS and Higher Overall Response Rates in Patients with Renal Impairment Treated With XVd vs. Vd

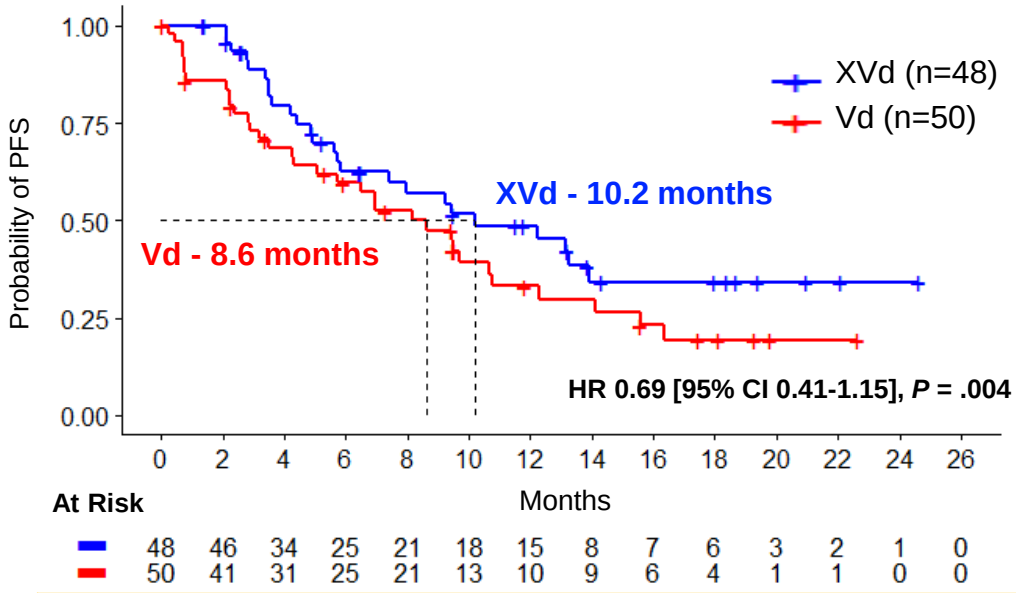


These subgroup analyses were exploratory in nature, not included in the study objectives and do not control for type 1 error. The analyses were not powered or adjusted for multiplicity to assess efficacy outcomes across these subgroups.

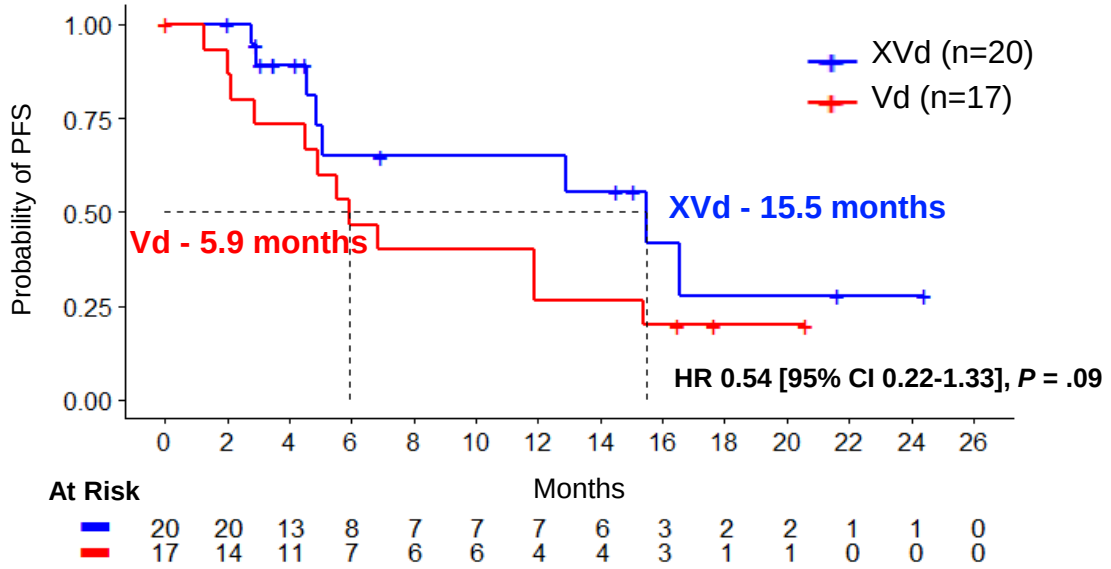
CI, confidence interval; HR, hazard ratio; PFS, progression free survival; Vd, bortezomib + dexamethasone; XVd, selinexor + bortezomib + dexamethasone.
Data on file (KPTSC1011).

Data Demonstrated a Statistically Significant Longer PFS in Patients with High-Risk Cytogenetics Treated With XVd vs. Vd

PFS in Patients With 1 Cytogenetic Abnormality



PFS in Patients With ≥2 Cytogenetic Abnormalities

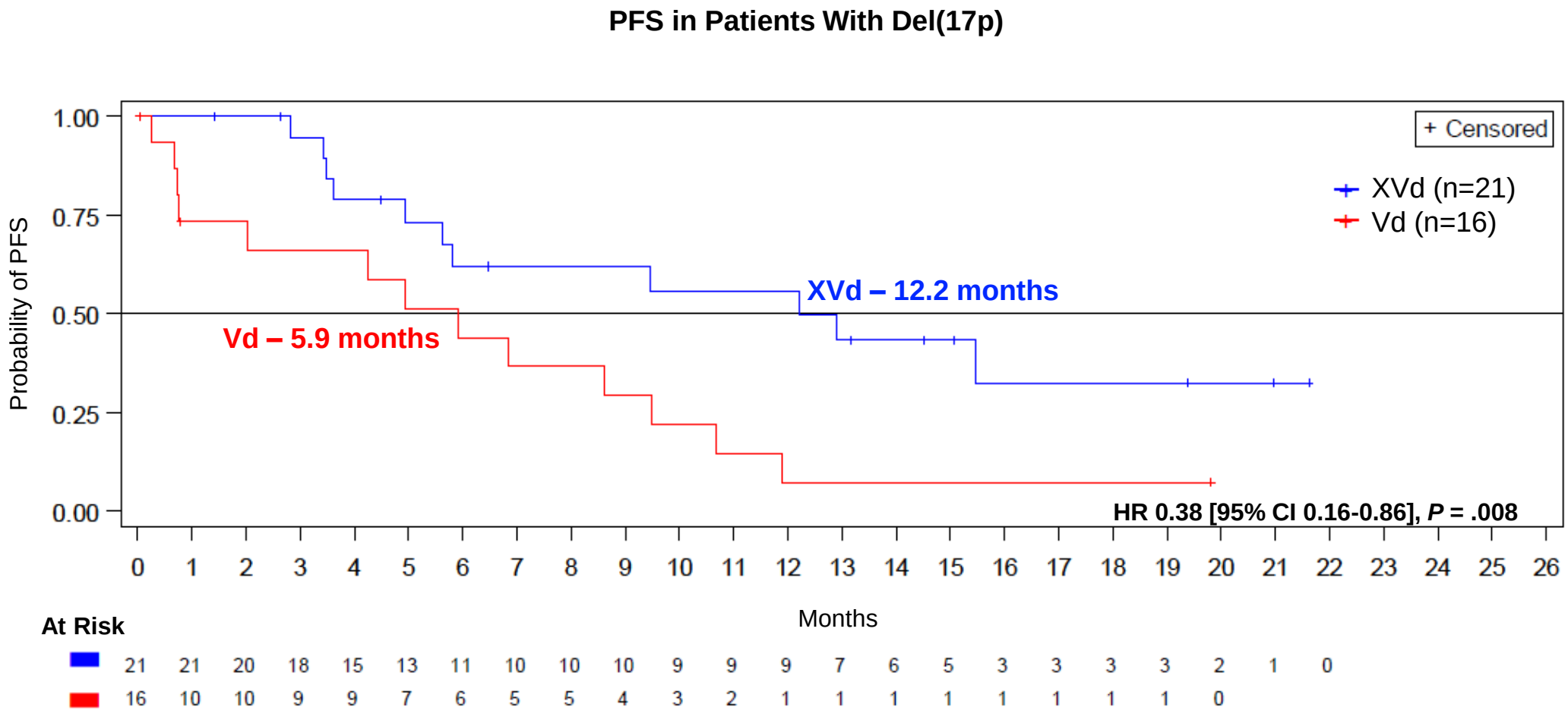


	Standard Risk		All High Risk		Del (17p)		t(4;14)		t(4;16)		Amp (1q21) ≥4 copies	
Treatment Arm	XVd	Vd	XVd	Vd	XVd	Vd	XVd	Vd	XVd	Vd	XVd	Vd
No. of Patients	125	136	70	71	21	16	22	27	7	11	43	39
PFS, years	16.62	9.46	12.91	8.61	12.22	5.91	13.24	8.33	4.57	11.89	12.91	8.15
HR (*P* value)	0.61 (0.004)		0.73 (0.08)		0.38 (0.009)		0.70 (0.18)		1.46 (0.75)		0.63 (0.07)	
ORR, %	75.2	64.7	78.6	57.7	76.2	37.5	90.9	74.1	85.7	54.5	76.7	61.5
P value	0.03		0.004		0.0096		0.07		0.09		0.07	

These subgroup analyses were exploratory in nature, not included in the study objectives and do not control for type 1 error. The analyses were not powered or adjusted for multiplicity to assess efficacy outcomes across these subgroups.

CI, confidence interval; HR, hazard ratio; ORR, overall response rate; PFS, progression free survival; Vd, bortezomib + dexamethasone; XVd, selinexor + bortezomib + dexamethasone.
Richard S, et al. Presented at the American Society for Hematology Annual Meeting; December 5-8, 2020. Abstract 1385.

Data Demonstrated Longer PFS in Patients With Del(17p) Treated With XVd vs. Vd



These subgroup analyses were exploratory in nature, not included in the study objectives and do not control for type 1 error. The analyses were not powered or adjusted for multiplicity to assess efficacy outcomes across these subgroups.

CI, confidence interval; HR, hazard ratio; PFS, progression free survival; Vd, bortezomib + dexamethasone; XVd, selinexor + bortezomib + dexamethasone.
Data on file (KPTSC1012).

Adverse event profiles of MM regimens

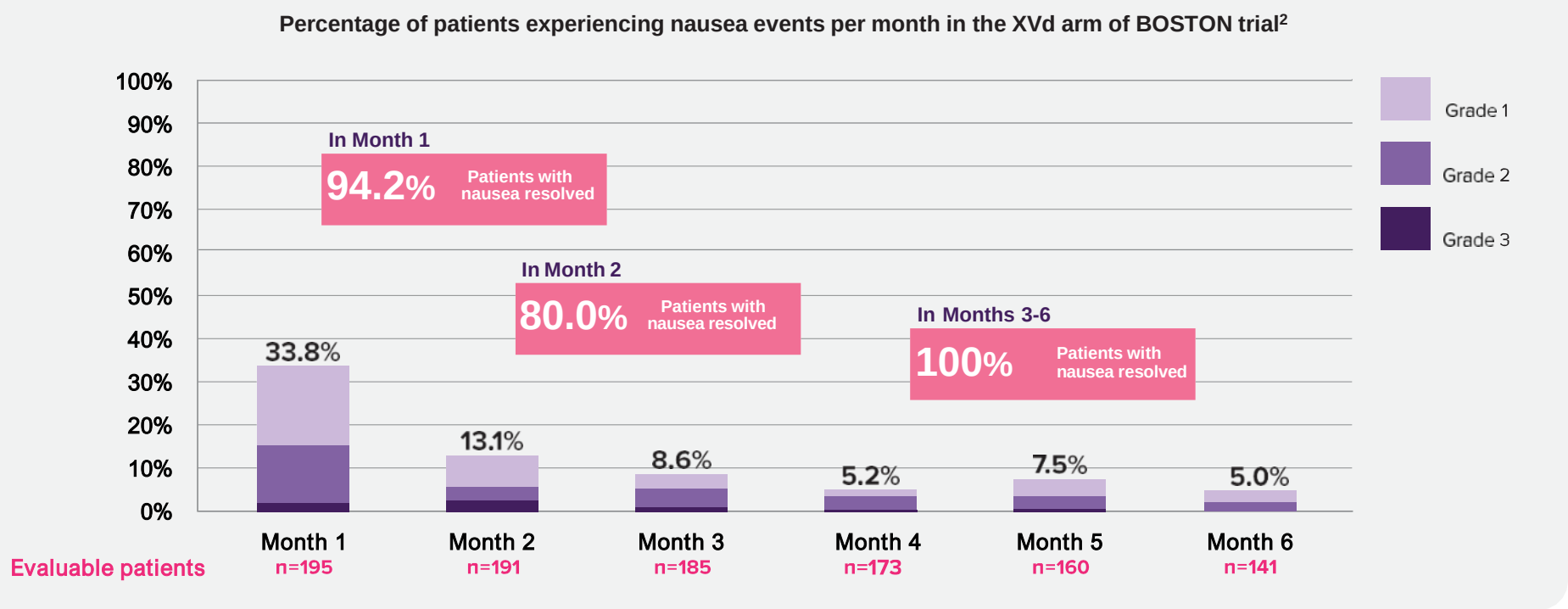
Selinexor +bortezomib +dexamethasone[1]	**GI:** Nausea, diarrhoea	**Haematologic:** Thrombocytopenia, anaemia, neutropenia	**General:** Fatigue, asthenia, decreased appetite, pneumonia
Isatuximab +carfilzomib +dexamethasone[2]	**Infusion reactions**	**GI:** diarrhoea	**Haematologic:** Anaemia, neutropenia, thrombocytopenia	**General:** Hypertension, RTI, fatigue, dyspnea, pneumonia
Belantamab mafodotin +bortezomib +dexamethasone[3]	**Ocular:** Keratopathy/microcyst-like epithelial changes	**Infusion reactions**	**Haematologic:** Thrombocytopenia, anaemia
CAR T-cell therapy[5]	**Cytokine release syndrome**	**Neurotoxicity**	**Haematologic:** Cytopenias

CAR, chimeric antigen receptor; GI, gastrointestinal; MM, multiple myeloma; RTI, respiratory tract infection.

1. Grosicki S, et al. *Lancet*. 2020;396:1563–73; 2. Moreau P, et al. *Lancet*. 2021;397:2361–71. 3. Nooka A, et al. Oral presentation at ASCO 2020; 8502.
4. Hajek R, et al. *J Clin Oncol*. 2021;39 (suppl 1):abstract 8037; 5. Zhou X, et al. *Front Immunol.* 2020;11:620312.

Treatment-related nausea with XVd is generally manageable and transient[1]

- Percentage of patients experiencing nausea decreased in the first month of XVd using appropriate antiemetic measures



In the BOSTON trial, nausea events were observed in 50% of patients (8% Grade 3).[1]

The median dosage in the BOSTON trial was 80 mg (range 30-137 mg) taken weekly.[1]

The BOSTON trial protocol required a prophylactic 5-HT3 antagonist to address nausea but allowed for other interventions as required.

IMPORTANT SAFETY INFORMATION

- XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia was reported in patients with multiple myeloma.

References: 1. XPOVIO. Prescribing information. Karyopharm Therapeutics Inc; 2021.

XPOVIO Dosing has been Continually Refined Over Time to Improve Efficacy and Patient Experience from High Dose BIW to Low Dose QW

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

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

IN THE BOSTON STUDY

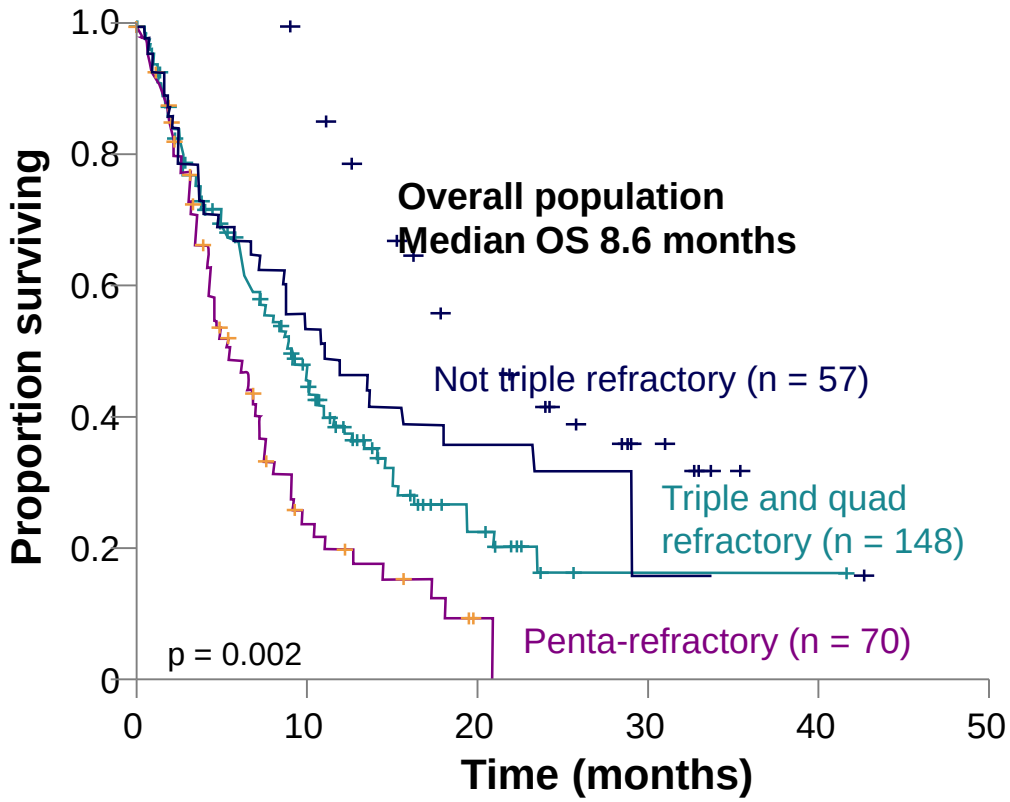
- 65% of patients in the XVd arm had an XPOVIO dose reduction (126/195 patients) vs 35% of those without a dose reduction (69/105)
- The median dosage was 80mg (range: 30-137 mg) taken once weekly
- Patients had their dosages reduced to mitigate adverse reactions (ARs)

*STOMP was designed to study XPOVIO 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.

MAMMOTH study: suboptimal outcomes in disease refractory to anti-CD38 monoclonal antibodies

275 patients refractory to anti-CD38 mAbs

	Median OS months	
Not triple refractory	11.2	Refractory to 1 CD38 mAb, and not both PI and IMiD
Triple and quad refractory	9.2	Refractory to 1 CD38 mAb + 1 PI + 1 or 2 IMiD compounds, etc.
Penta refractory	5.6	Refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds
Overall cohort	8.6	



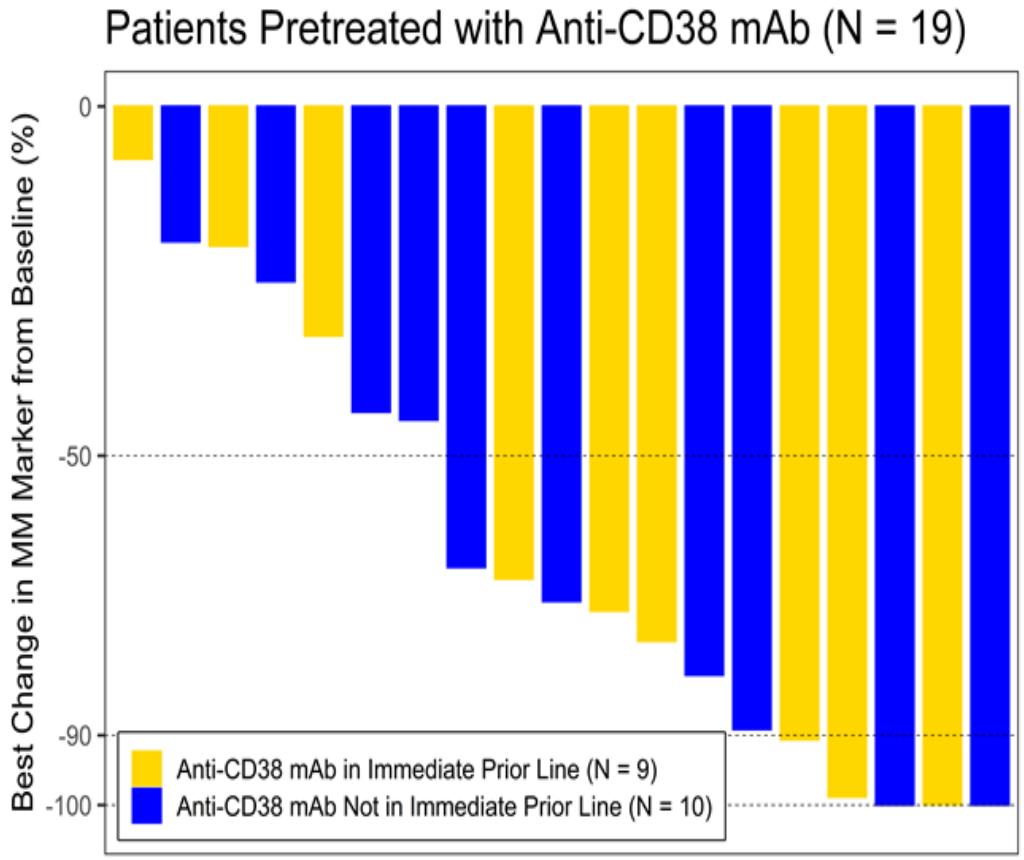
249 patients received further treatment
ORR 31%
Median PFS 3.4 months
Median OS 9.3 months

Gandhi UH et al., *Leukemia*. 2019

All Oral Selinexor, Pomalidomide, and Dexamethasone (SPd) in RRMM is active with durable response post anti-CD38mAb based regimen

Best Responses in Evaluable SPd Patients

	N	ORR (%)	CBR (%)	>CR (%)	VGPR (%)	PR (%)
RP2D: Selinexor 60 mg QW + Pom 4 mg	20	13 (65.0)	15 (75.0)	1(5.0)	5 (25.0)	7 (35.0)
Prior Anti-CD38 mAb	19	11 (57.9)	14 (73.7)	1 (5.)	3 (15.8)	7 (36.8)



Conclusions:

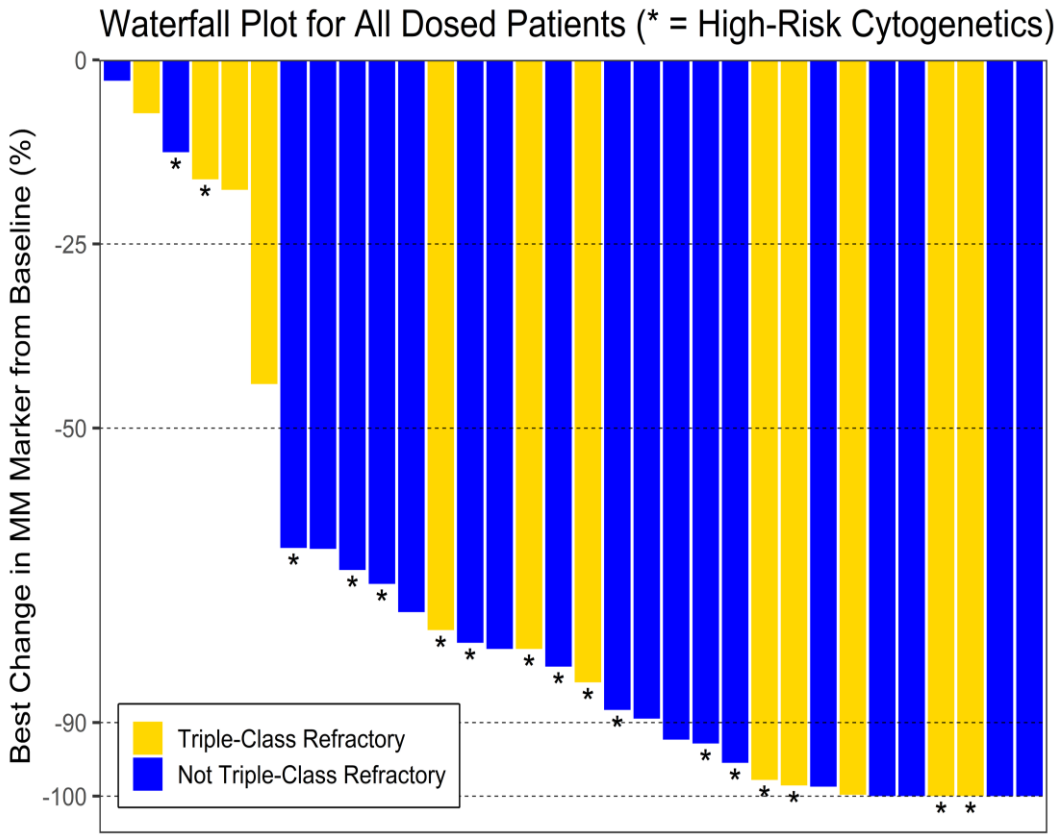
- PFS: 12.2 months for Pom Naïve (10.4 months for all patients)
- ORR: 57.9% post anti-CD38 mAb
- SPd is active post anti-CD38 with high ORR and durable response

Once Weekly Selinexor, Carfilzomib, and Dexamethasone (SKd) is a highly active combination

(Selinexor 80 mg QW + Carfilzomib 56 mg/m^2)

Best Responses in Evaluable SKd Patients

	N	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR (%)
Overall	32	25 (78.1)	26 (81.3)	5 (15.6)	8 (25.0)	12 (37.5)
Prior lines of therapy						
1 – 2	8	**7 (87.5)**	7 (87.5)	3 (37.5)	3 (37.5)	1 (12.5)
≥ 3	23	17 (73.9)	18 (78.3)	2 (8.7)	5 (21.7)	10 (43.5)
High-risk cytogenetics†						
No	15	11 (73.3)	11 (73.3)	4 (26.7)	3 (20.0)	4 (26.7)
Yes	17	14 (82.4)	15 (88.2)	1 (5.9)	5 (29.4)	8 (47.1)



Conclusion:

- **SKd is highly active combination with an ORR of 78%, with impressive ORR of 87.5% in patients with 1-2 priors**
- SKd is active post an anti-CD38 mAb with an ORR of 68% with a PFS of 15 months
- SKd is active in patient with high-risk MM

Conclusions

1. Selinexor-based regimens are highly active post anti-CD38 treatment
2. Additional patient benefit seen in important sub-populations, including older/frail, renal insufficiency and high-risk cytogenetics
3. Evolved dosing results in a more manageable and tolerable patient experience

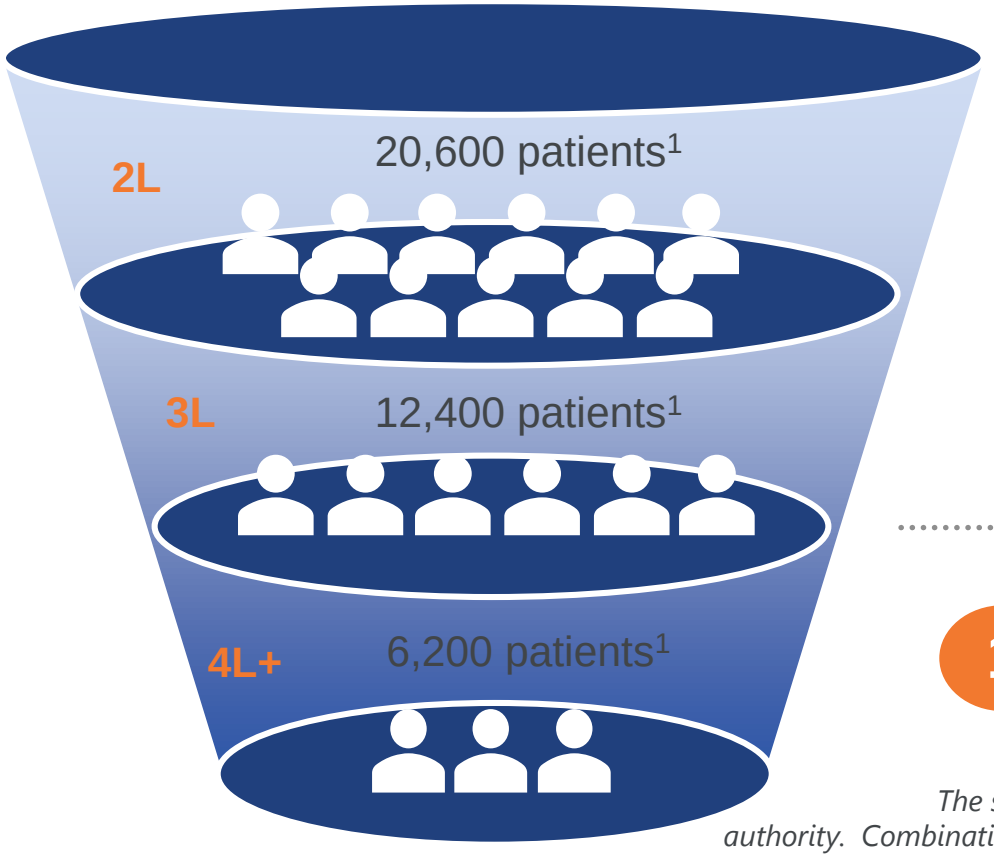
MULTIPLE MYELOMA COMMERCIAL OPPORTUNITY AND WRAP UP

Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
SVP, Sales and Commercial Operations

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

~40,000 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.

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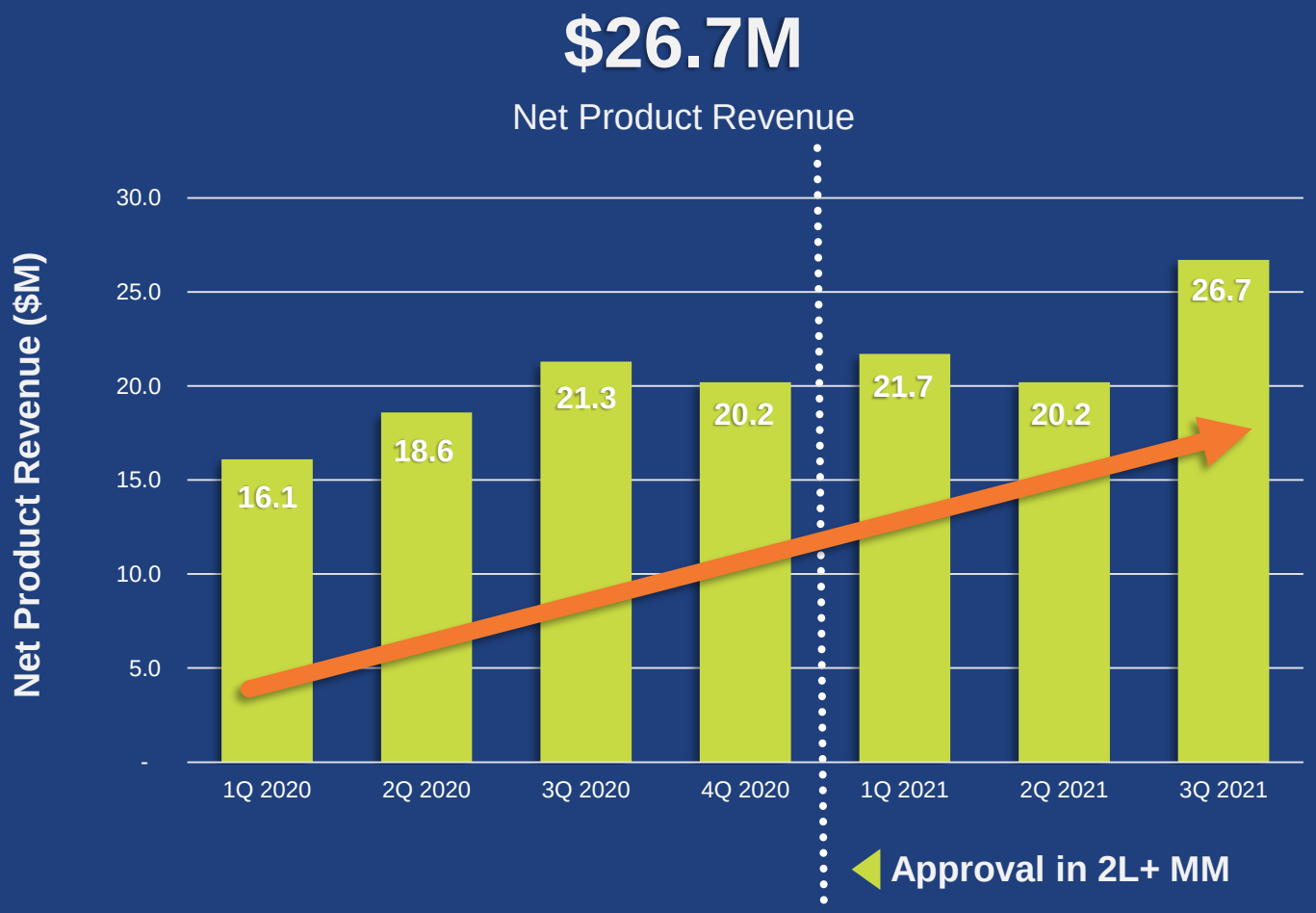
1. Kantar CancerMPact

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
- Increased uptake in earlier lines[1]
- Double digit growth in demand in community and improvement in intent-to-prescribe metrics
- Evolution of patients to lower dose with >90% of patients on 100mg or lower starting dose

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

Evaluation of SPd Registration Enabling Study, Builds on Well-established Backbone in 2L+ and Serves as an All-Oral Regimen

SPd

1. **UNMET NEED POST ANTI-CD38:** ~80% patients exposed to an anti-CD38 in 1L-2L, with an unmet need for a new class of therapy[1]
2. **ALL-ORAL:** Oral class is highly preferred with >50% 2L regimens containing an oral drug[1]
3. **COMPELLING PRODUCT PROFILE:** STOMP data showed a PFS of 10.4 months for all patients and 12.2 months for Pom Naïve; well tolerated
4. **COMBINATION WITH WELL ESTABLISHED BACKBONE:** Increasing use of Pomalyst based triplets, accounting for >20% of new patient starts in 2L-3L[1]

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.

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1. BrandImpact Sep 2021

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

Growing Market Opportunity

- ~40,000 patients per year in the 2L+[1]
- 2L and 3L growing by 2.3% year-over-year[2]
- ~80% patients exposed to an anti-CD38 in 1L-2L, with an unmet need for a new class of therapy[3]

Competitively Well-positioned

- New MOA
- Proven efficacy in post-anti CD38 setting with 2 years on the market and >9,000 prescriptions filled
- Potential combinability with multiple backbones
- Generally manageable safety profile

Critical Growth Drivers for 2022

- Strong execution of post-anti CD38 messaging in 2L+ with focus on live physician engagements
- Continue to shift into earlier line use
- Increase breadth and depth of account adoption
- Build physician confidence with focus on community physicians through optimal patient management

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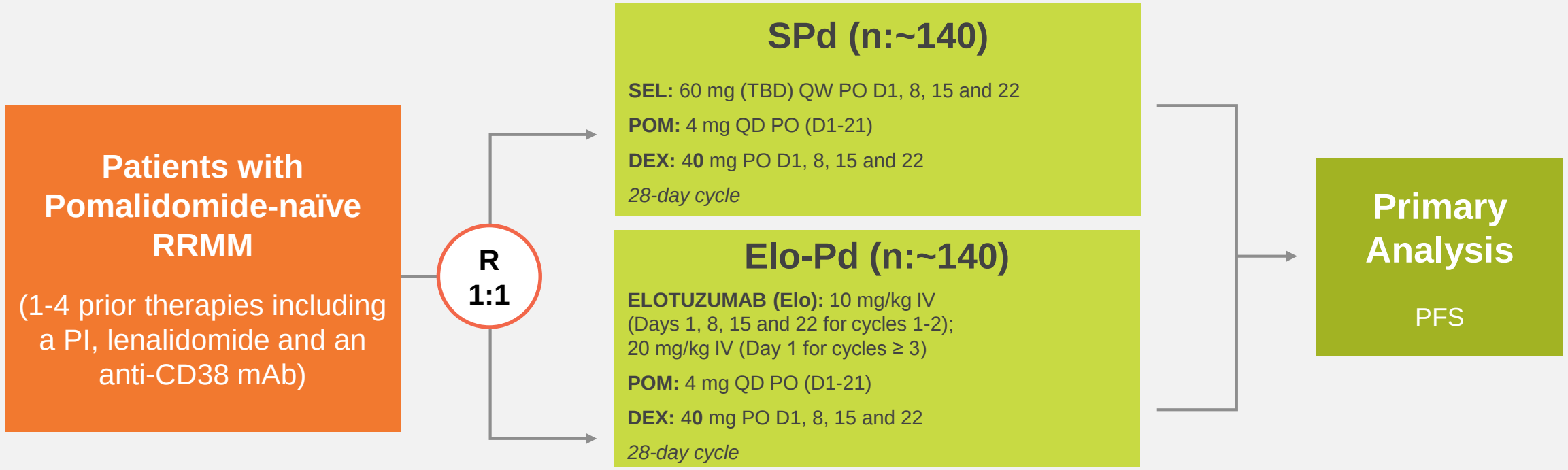
1. Kantar CancerMPact. **2.** Clarivate/DRG Epidemiology Data. **3.** BrandImpact Sept 2021.

Phase 3 Study Evaluating Selinexor, Pomalidomide and Dexamethasone (SPd) in Patients with Previously Treated Multiple Myeloma[1]



Expect to dose first patient in 1Q 2022

Top-line data expected 2024

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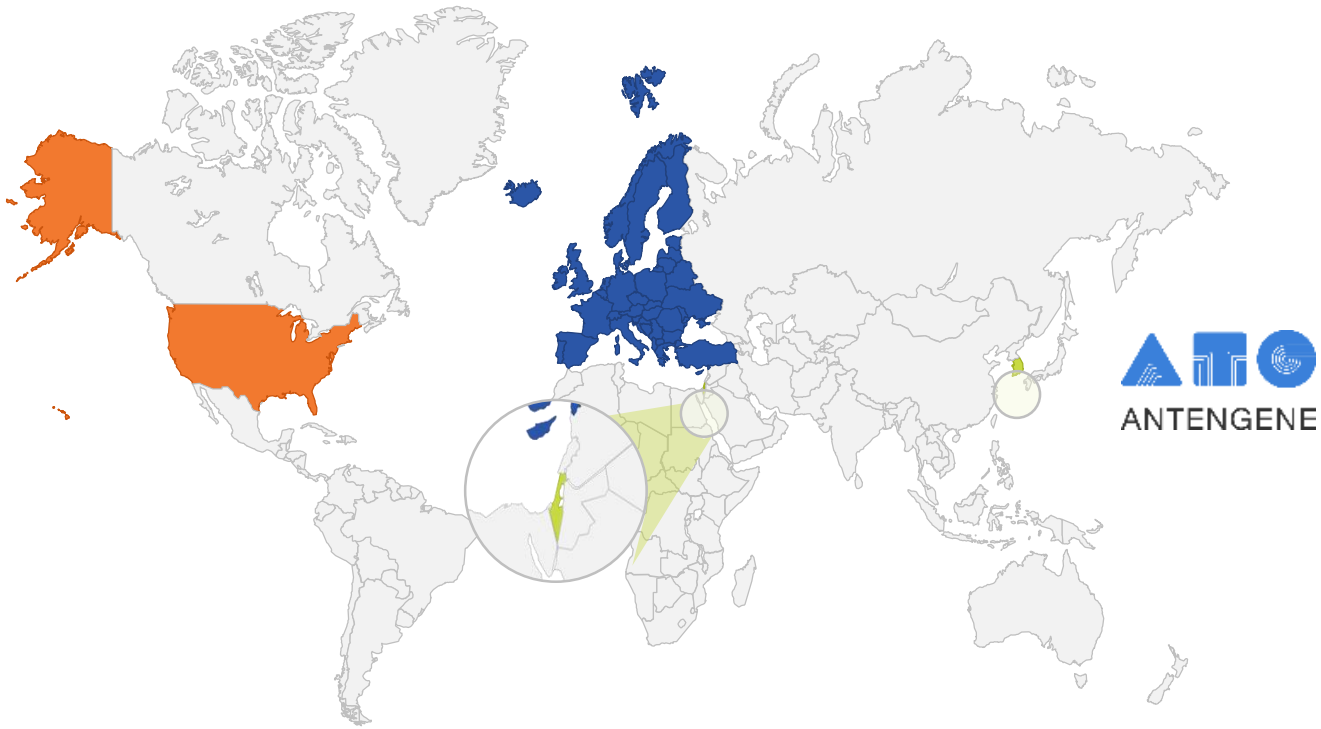
1. XPORT-MM-031

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]



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

Selinexor in Multiple Myeloma: Key Takeaways

1. **Addressing significant unmet need for 2L+ multiple myeloma patients where an effective new class of therapies is needed**

2. **XPOVIO-based combinations striving to become a new standard of care with critical need for efficacious, novel combinations post anti-CD38** (complimentary to IMiDs, PIs and CAR-T) **and high-risk cytogenetics**

3. **Building confidence with key prescribers with evolving XPOVIO dose and improved patient experience**

4. **Evolving into broader MM opportunities, including all oral with SPd**
(e.g., penta-refractory to 2L+, new combinations with approved agents, etc.)

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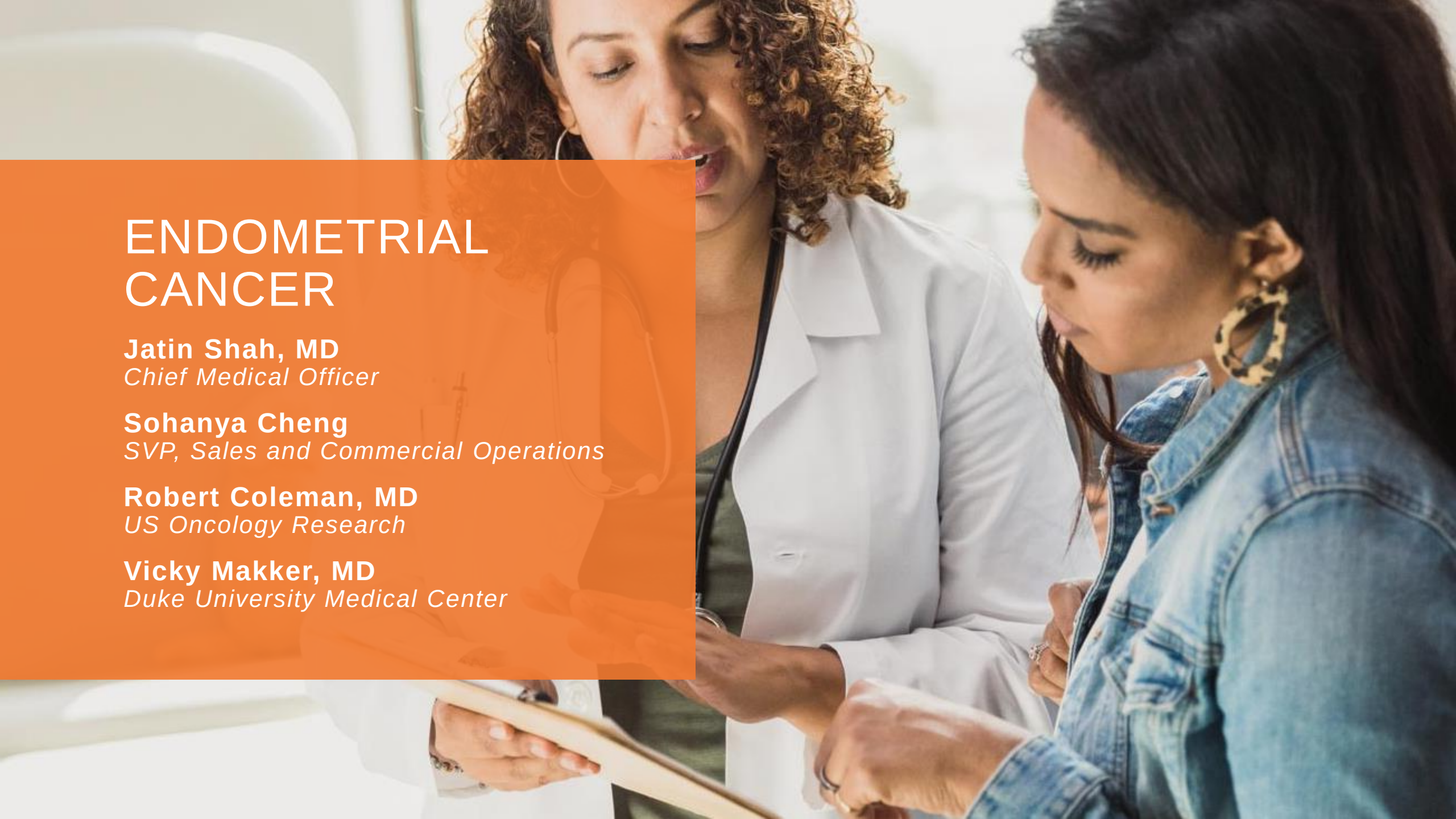
MULTIPLE MYELOMA

Q&A



ENDOMETRIAL CANCER

Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
SVP, Sales and Commercial Operations

Robert Coleman, MD
US Oncology Research

Vicky Makker, MD
Duke University Medical Center

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

MULTIPLE MYELOMA

~40,000 patients (2L+)[1,5]

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

ENDOMETRIAL CANCER

~14,000 frontline patients[2,5]

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

MYELODYSPLASTIC SYNDROMES

~15,000 intermediate to high-risk patients[3,5]

Potential to improve survival in HMA-refractory MDS

MYELOFIBROSIS

~5,000 MF patients[4,5]

Potential to improve patient outcomes in JAKi-refractory MF

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1. Kantar Cancer Impact. **2.** Sorbe, B et al. Int J Gynecol Cancer 2008. **3.** Clarivate/DRG Epidemiology Data. **4.** https://my.clevelandclinic.org/health/diseases/15672-myelofibrosis. **5.** Annual U.S. incidence.

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

What is Endometrial Cancer?

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

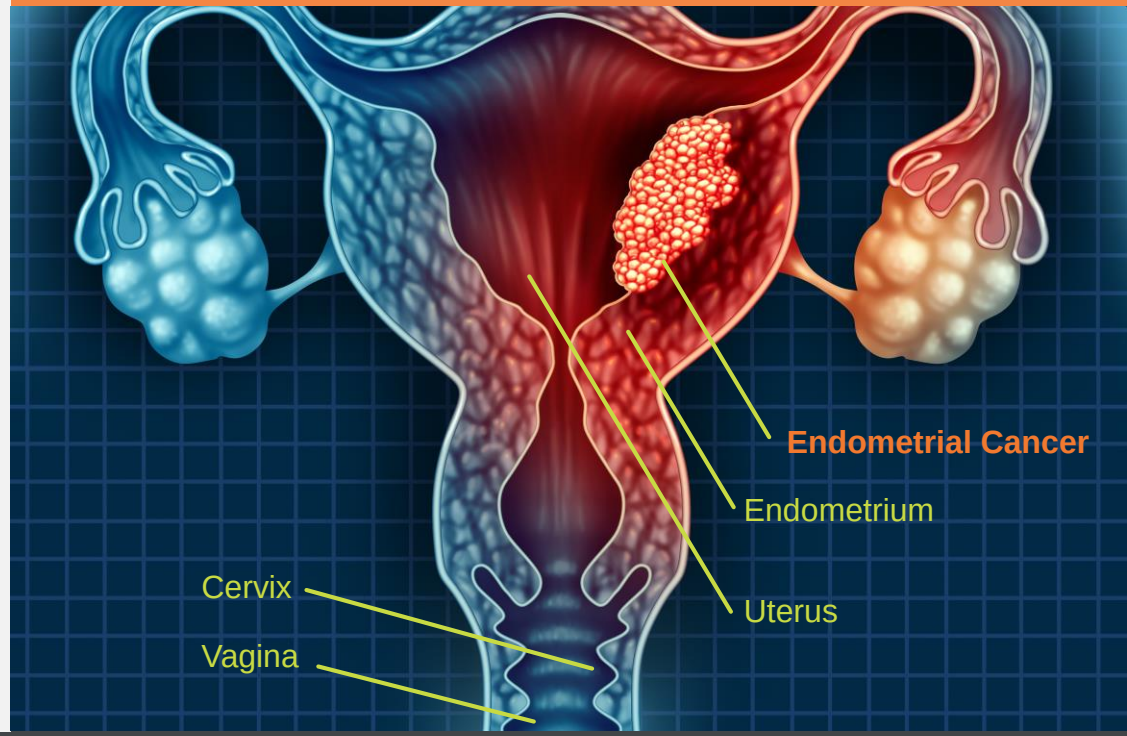
Treatment Landscape

- First-line treatment is chemotherapy (taxane plus platinum), where response rates (CR or PR) can be as high as 67%[1]
- Following chemotherapy, NCCN Guidelines® recommend “watch and wait” until disease relapses[2]

Opportunity and Unmet Need

- Prognosis is poor, with **progression expected within 4-6** months following first-line chemotherapy treatment
- No SoC or FDA-approved agent for maintaining response in EC post-systemic treatment to prevent or delay progression to later lines of treatment

The most common gynecological cancer in the US[3]



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.

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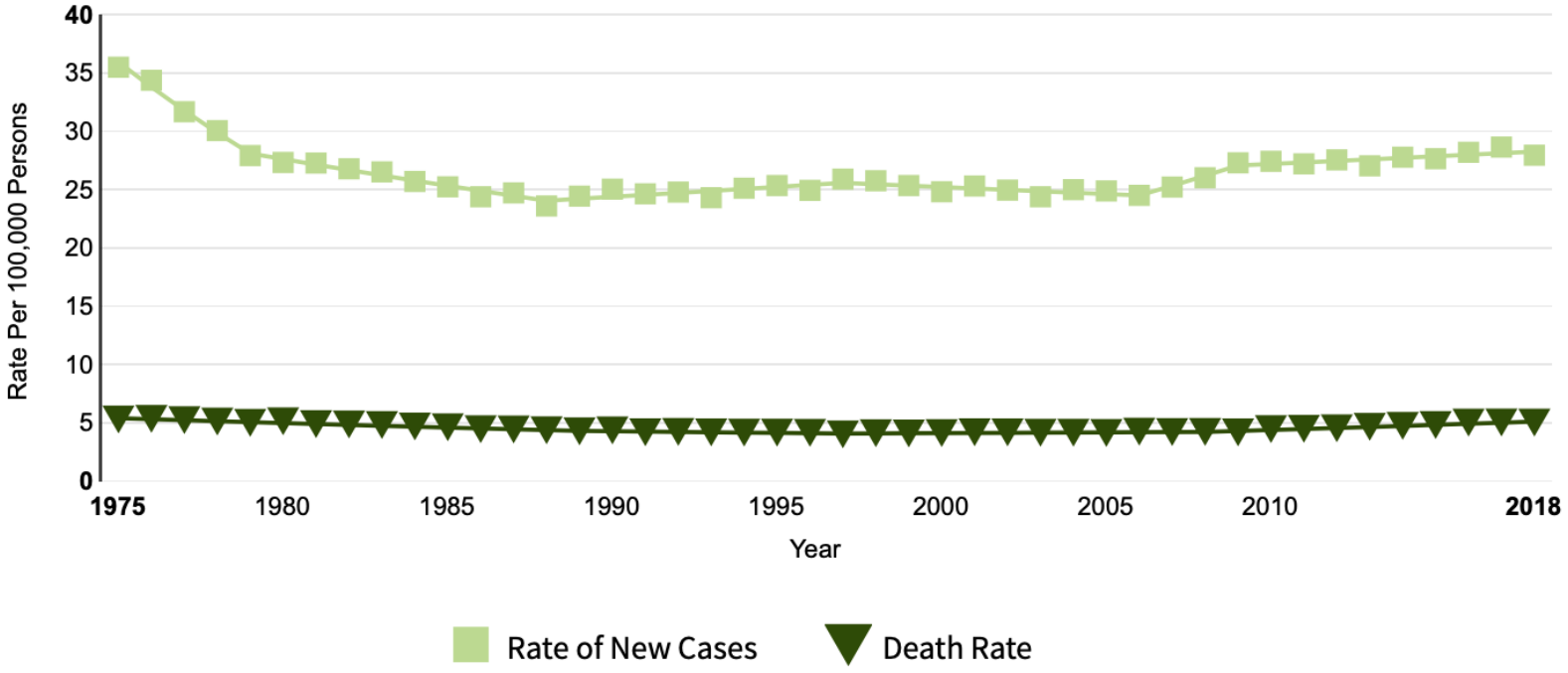
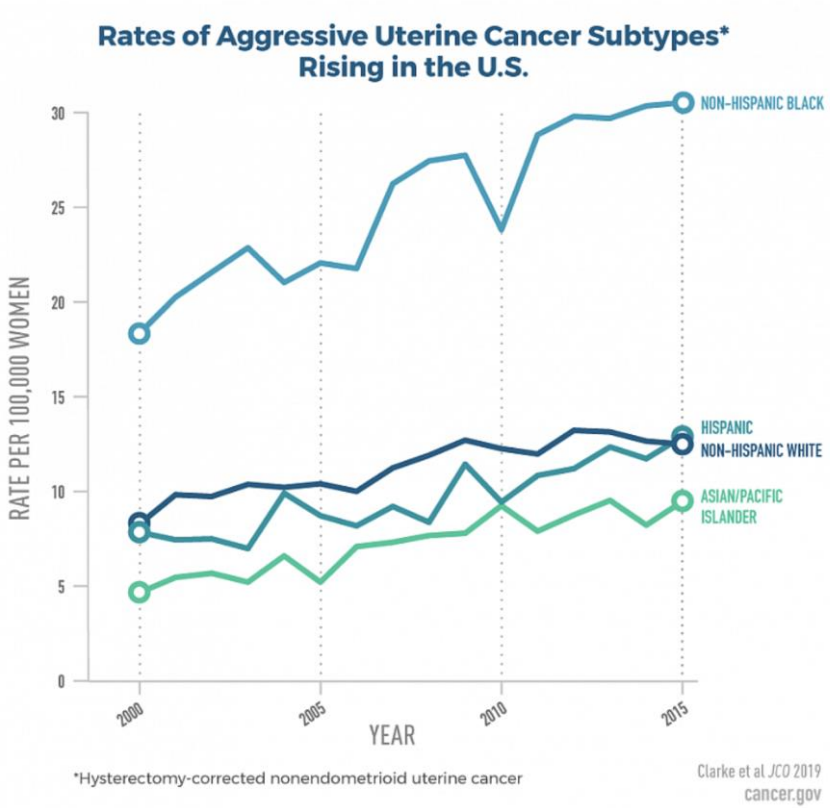
1. Sorbe, B et al. Int J Gynecol Cancer. 2008). **2.** National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Uterine Neoplasms. v4.2021. September 3, 2021; www.nccn.org. **3.** www.hopkinsmedicine.org/health/conditions-and-diseases/endometrial-cancer.

Endometrial Cancer: Therapeutic Landscape 2021

Robert L. Coleman, MD, FACOG, FACS
Gynecologic Oncologist & Chief Scientific Officer
US Oncology Research
The Woodlands, TX

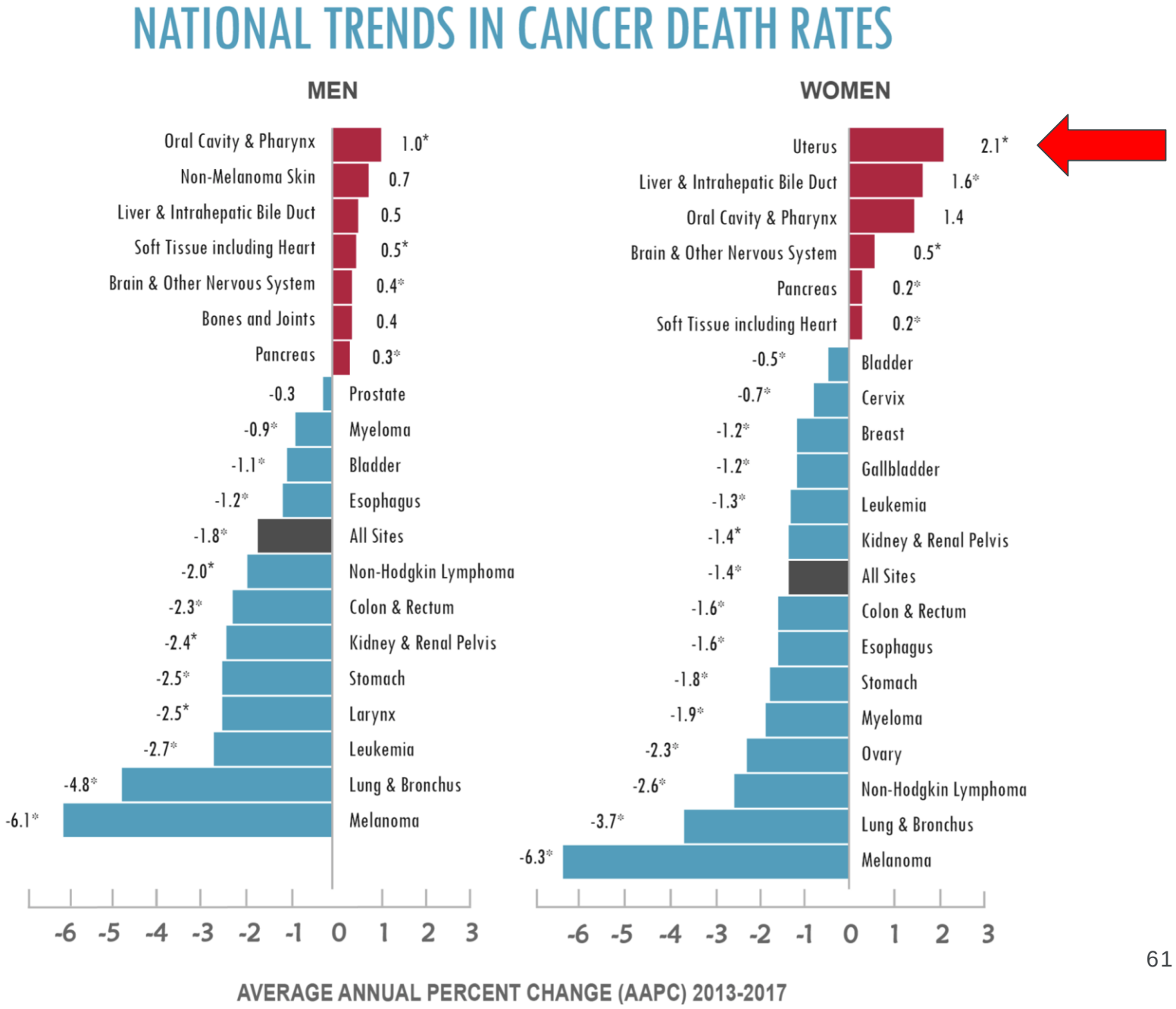
Cancer Facts: Natural History





National Cancer Institute. SEER Cancer Stat Facts: Uterine Cancer 2021. https://seer.cancer.gov/statfacts/html/corp.html. Published April 2018. Accessed January 8, 2019;

Cancer Facts: Natural History



NCI. https://seer.cancer.gov/statfacts/html/corp.html. Published April 2021. Accessed June 3, 2021.

Types of Endometrial Cancer: Traditional Model

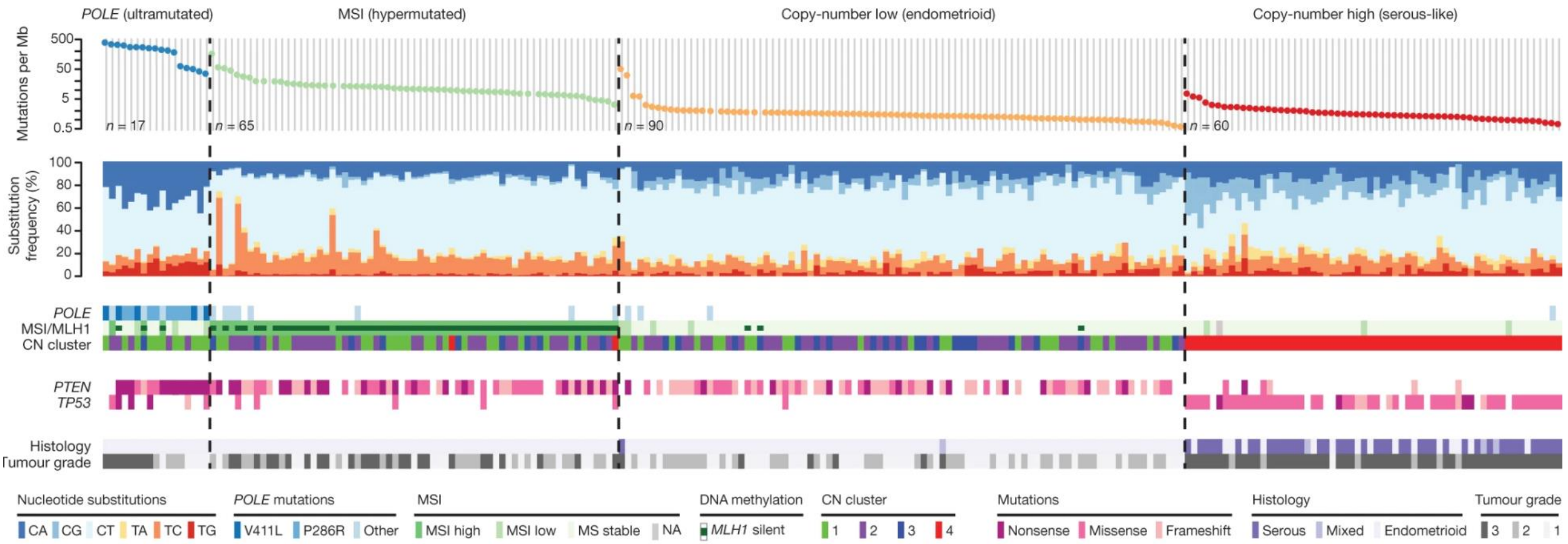
Type 1

- Estrogen driven
- Caucasian
- Typically, early stage
- Histology:
  - Well differentiated endometrioid
- Favorable prognosis

Type 2

- Age greatest risk factor
- Black/Asian
- Typically, advanced stage
- Histology:
  - Poorly differentiated or non-endometrioid
- Unfavorable prognosis

Contemporary Model: Molecular Characterization



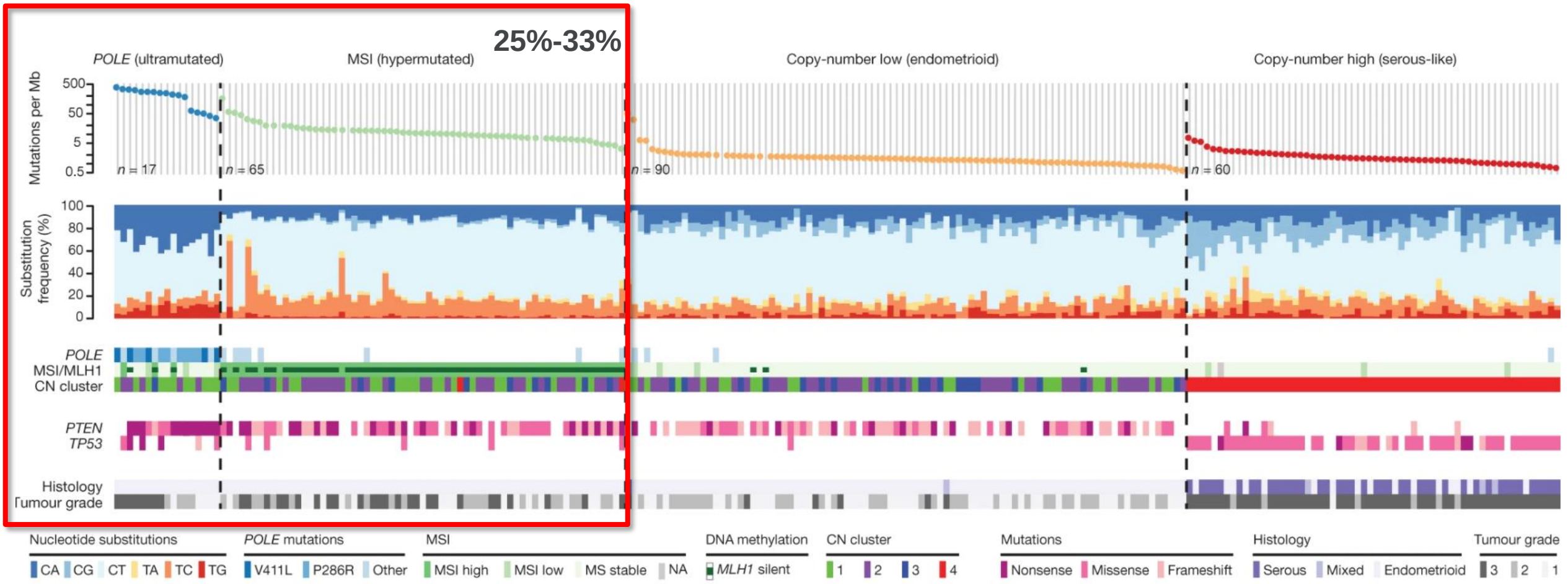
Kandoth Nature 2013

Endometrial Cancer: Therapeutic Strategy

- **Hormonal**
  - ER/PR axis known relevant for regulation of normal and abnormal epithelial growth
- **Chemotherapy**
  - Modality increasingly recognized as an important therapeutic option
  - “Chemo-sensitive” disease
- **Biologics**
  - Therapy based on characteristics of important signaling pathways

Alteration	Endometrioid (%)	Non-endometrioid (%)
PTEN protein loss[18,19]	80	5
PTEN mutation[15-17,25]	30–50	0–11
PIK3CA mutation[20,21,25]	30–40	20
PIK3R1 mutation[157]	43	12
AKT mutation[10,13,14]	2–3	0
KRAS mutation[54-57]	10–30	0–10
IGFIR overexpression[69,70]	78	Unknown
FGFR2 mutation[11,87,88]	12–16	1
EGFR overexpression[9,111]	46	34
EGFR mutation[113,114]	Unknown	0
HER-2 overexpression[9,111,124-126]	3–10	32
HER-2 amplification[124,126]	1	17
β-catenin mutation[133,134]	15–50	0
p53 mutation[158]	20	90
E-cadherin loss[129,130,133]	5–50	60–90
Microsatellite instability[159,160]	15–25	0–5

Newest Defining Therapeutic Indicator: Immunotherapy



Kandoth Nature 2013

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

FDA grants accelerated approval to dostarlimab-gxly for dMMR endometrial cancer

Share Tweet Linkedin Email Print

On April 22, 2021, the Food and Drug Administration granted accelerated approval to dostarlimab-gxly (Jemperli, GlaxoSmithKline LLC) for adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following a prior platinum-containing regimen.

FDA grants regular approval to pembrolizumab and lenvatinib for advanced endometrial carcinoma

Share Tweet Linkedin Email Print

On July 21, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) in combination with lenvatinib (Lenvima, Eisai) for patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

FDA granted accelerated approval on September 17, 2019 to pembrolizumab with lenvatinib for advanced endometrial carcinoma. Study 309/KEYNOTE-775 (NCT03517449) was a multicenter, open-label, randomized, active-controlled trial

Content current as of:
07/22/2021

Regulated Product(s)
Drugs
Prescription Drugs

Contemporary Landscape for Treatment

Clinical Situation	Treatment (current)	Treatment Opportunity
Newly diagnosed metastatic (Her2neu)	Chemotherapy (+anti-ErbB2)	Adjuvant immunotherapy (MSI-H, MSS) **Novel agents: Selinexor**
Recurrent (no prior or adjuvant chemo)	Chemotherapy (+anti-ErbB2 if naive)	Replace chemo: Len/pem (MSS), pem (MSI-H) Adjuvant immunotherapy (if naïve) Adjuvant immunotherapy combinations **Novel agents: Selinexor,** PARPi
Recurrent (prior chemo)	Single agent chemo or Pembro (MSI-H, TMB-H) Len/Pem (MSS) endocrine	Novel agents (molecularly defined)

Endometrial Cancer: Current Treatment Landscape

Vicky Makker, MD

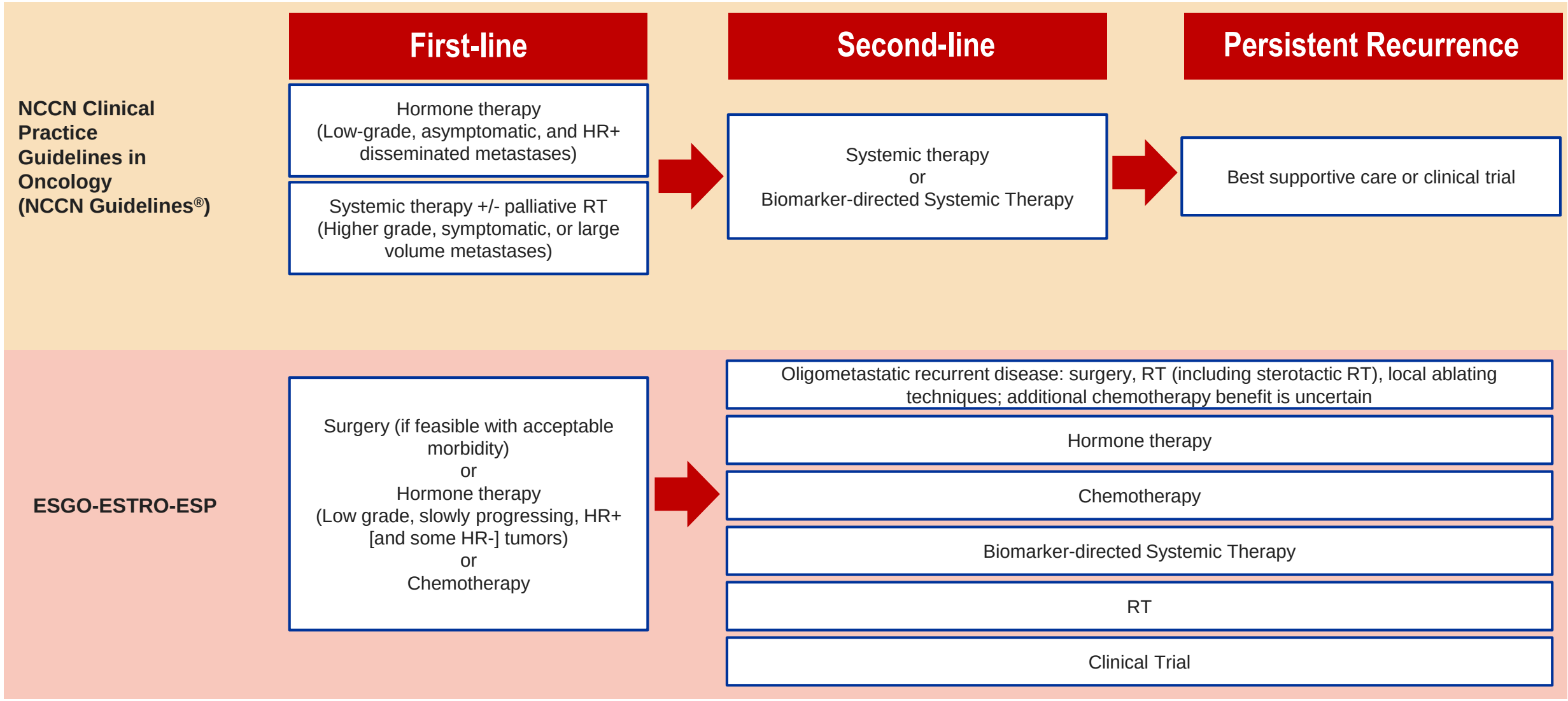
Memorial Sloan Kettering Cancer Center

Associate Attending Physician

Gynecologic Medical Oncology Service

Section Head Endometrial Cancer

Endometrial Cancer Treatment Landscape



Chemotherapy for Advanced/Recurrent EC —UNMET NEED EXISTS

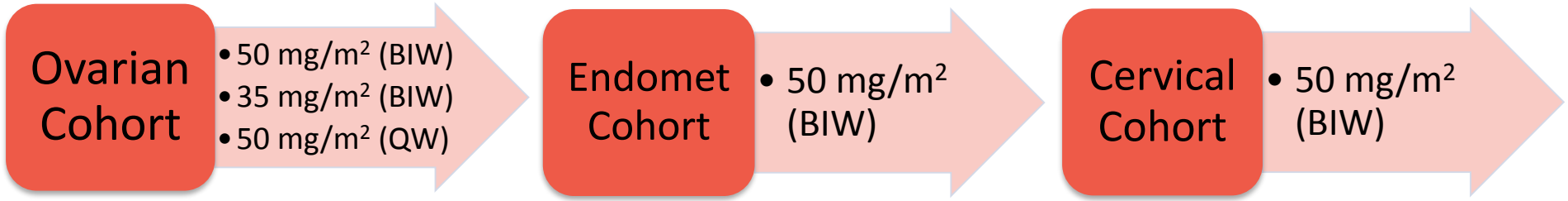
- First Line - combination
  - RR ~ 50%
  - PFS: 8 - 14 months (including ~6 months on chemotherapy)
  - OS: 32 - 38 months
- Second Line – single agents
  - RR ~ 15-30%
  - PFS: 3 months
  - OS: 6 – 12 months

Fleming GF. *J Clin Oncol.* 2004;22:2159-2166, Miller D SGO late breaking abstract #1

Selinexor in Endometrial Cancer

Selinexor In Gynecological Neoplasms (SIGN) Phase II Study Design

- **Primary Endpoint**:
  - **Disease control rate (DCR)** *complete or partial response, or stable disease for at least 12 weeks (SD≥12)*
    - Looking for ≥ 8 patients in the first 21 patients enrolled per cohort to reach DCR, which will warrant Phase III exploration
- **Main Inclusion Criteria**:
  - Patients ≥18 years old, ECOG performance status 0-1, Life expectancy ≥12 weeks
  - Ovarian patients – **Platinum refractory/resistant** patients, ≥1 prior chemotherapy line
  - Endometrial/Cervical patients – **≥1 line of chemotherapy** for relapsed or advanced disease
- **Treatment Scheme**: Twice Weekly (BIW) or Once Weekly Dosing (QW) / 28-day cycle



SIGN: Phase 2 Open-Label, Multicenter, Two-Stage Study in Advanced or Metastatic Gynecological Malignancies

- Study enrolled patients with ovarian cancer, endometrial cancer or cervical cancer.
- Participants had a median age of 63 years (31-80) and received a median of 4 prior therapies (range 1-11).
- Nearly all patients had prior platinum-based chemotherapy (52% refractory) and taxane.
- Disease control was higher in patients with endometrial cancer (35%).
- Three of 23 patients with endometrial cancer (13%) achieved a PR.
- The median duration of stable disease for patients with endometrial was 6.3 months.
- Patients with disease control had markedly improved overall survival (OS) compared to patients without disease control.
- In the cohorts with endometrial cancer, patients with disease control had a median OS of 20.4 months, versus 3.9 months for patients without disease control.
- No new AEs or SAEs observed and consistent with label.

Selinexor with Paclitaxel and Carboplatin in Ovarian or Endometrial Cancers

- IST study, *NCT02269293,* PI: Dr. Makker

Purpose:
Evaluate safety and tolerability of oral selinexor plus intravenous carboplatin and paclitaxel chemotherapy (selinexor + CP).

Patients:

- Ovarian cancer patients who have received 1 prior platinum-based therapy (n=5)
- Endometrial cancer patients that chemotherapy naïve or had received 1 prior platinum-based therapy (n=18)

Methods:

- Phase I, 3+3 dose-escalation, 4 dose regimens tested (3-week/cycle)

Regimen	Carbo*/Paclitaxel Dosing	Selinexor Dosing
1	Carbo + Every-3-Week Paclitaxel (175 mg/m^2)	30 mg/m^2, BIW
2	Carbo + Weekly (dose dense) Paclitaxel (80 mg/m^2)	30 mg/m^2, BIW
3	Carbo + Weekly (dose dense) Paclitaxel (80 mg/m^2)	60 mg, QW
4	Carbo + Every-3-Week Paclitaxel (175 mg/m^2)	60 mg, QW

***Carboplatin: AUC 5 IV, Day 1 per cycle**

Study Conclusion:

- Combination selinexor + CP was safe and tolerated in advanced ovarian and endometrial cancers.
- Selinexor RP2D defined as 60mg QW.

Rubinstein, MM et al, Gynecologic Oncology, 2021

Selinexor with Paclitaxel and Carboplatin in Ovarian or Endometrial Cancers, Including Multiple Subtypes

- Best Overall Response

Regimen	Tissue	Histology	Relapsed/Metastatic	Best Response
1	Ovary	HGSOC	relapsed	SD
1	Endometrial	Serous	metastatic	PR
1	Endometrial	Endometrioid, Grade 3 HGSOC	relapsed	PD
2	Ovary	HGSOC	relapsed	PR
2	Endometrial	Serous	metastatic	PR
2	Endometrial	Serous	relapsed	PR
2	Endometrial	Carcinosarcoma	relapsed	N/A
2	Endometrial	Endometrioid, Grade 3	relapsed	PR
2	Endometrial	Carcinosarcoma	relapsed	PR
2	Endometrial	Endometrioid, Grade 1	relapsed	PR
3	Ovary	HGSOC	relapsed	PR
3	Endometrial	Endometrioid, Grade 2	relapsed	PR
3	Ovary	HGSOC	relapsed	CR
3	Endometrial	Carcinosarcoma	relapsed	PR
3	Endometrial	High Grade, NOS	metastatic	PR
3	Endometrial	Carcinosarcoma	metastatic	PD
4	Endometrial	Serous	relapsed	SD
4	Endometrial	High grade, NOS	metastatic	PR
4	Endometrial	Carcinosarcoma	metastatic	PD
4	Ovary	HGSOC	metastatic	N/A
4	Endometrial	Endometrioid, Grade 2	metastatic	N/A
4	Endometrial	Carcinosarcoma	relapsed	PD
4	Endometrial	Endometrioid, Grade 3	metastatic	SD

HGSOC- high grade serous ovarian cancer, NOS-not otherwise specified, CR- complete response, PR- partial response, SD-stable disease, PD- progression of disease, N/A- not available.

Responses were noted in both newly diagnosed and platinum refractory patients

Regimen	Carbo/Paclitaxel Dosing	Patient number	Selinexor Dosing	ORR (CR + PR)
1	Carbo + Every-3-Week Paclitaxel	3	30 mg/m^2 BIW	**33%**
2	Carbo + Weekly Paclitaxel	7*	30 mg/m^2 BIW	**100%**
3	Carbo + Weekly Paclitaxel	6**	60 mg QW	**83%**
4	Carbo + Every-3-Week Paclitaxel	7	60 mg QW	**20%**

*6 endometrial patients, 3 (50%) are chemo sensitive
** 4 endometrial patients, 2 (50%) are chemo sensitive

➢ **Seli (60mg QW) + Paclitaxel (weekly dosing) is more efficacious**

Rubinstein, MM et al, Gynecologic Oncology, 2021

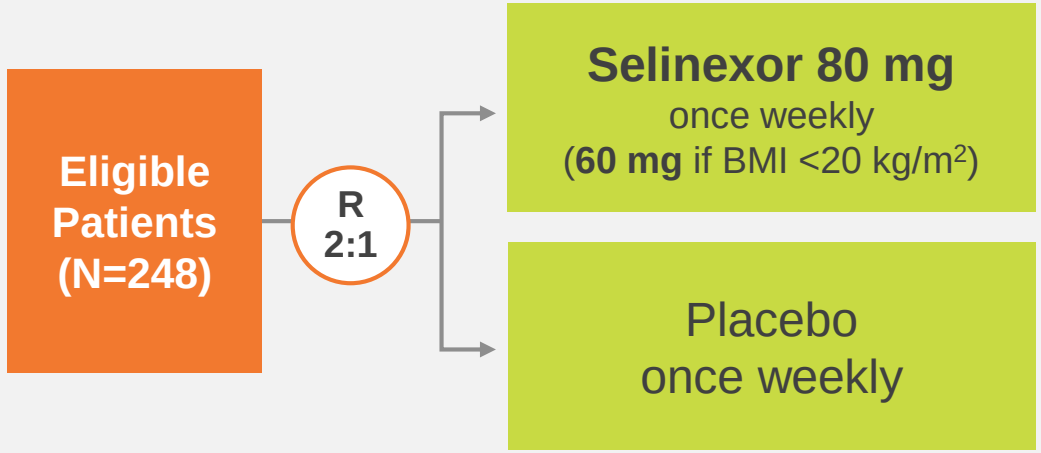
SIENDO Study Design:

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 from time of randomization until death or disease progression as determined by Investigator

Statistical Design

- HR 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

Completed recruitment December 2021

Top-line data expected in 1Q 2022

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ENDOMETRIAL CANCER COMMERCIAL OPPORTUNITY AND WRAP UP

Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
SVP, Sales and Commercial Operations

Selinexor Could be the First Approved Drug for the Maintenance of Advanced Endometrial Cancer, with the Potential to Extend Remission

Growing Market Opportunity

- Most common gynecologic cancer in the U.S with ~66K cases[1]
- Addressable market will grow with new and more effective therapies over time[2]
- ~14,000 frontline patients receiving chemotherapy with a growing addressable patient population in maintenance setting[3]

Competitively Well-positioned

- No approved drug therapies post chemotherapy in the maintenance setting to prolong response
- Promising results in a Phase 2 study (Vergote, 2019) in patients with progressing endometrial cancer (2L and later)

Critical Success Factors

- Deliver clinically significant results from SIENDO and rapidly engage FDA with sNDA
- Establish EC maintenance as SoC vs. “watch and wait” approach
- Leverage established field and access capabilities
- Engage opinion leaders and patient advocacy

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1. SEER / NCI Cancer Stat Facts. 2020. https://seer.cancer.gov/statfacts/html/corp.html. **2.** Decision Resources. **3.** Epic Oncology (Incidence, 1st/ 2nd line treated); epic Oncology physician survey 2019. **3.** Sorbe, B et al. Int J Gynecol Cancer 2008.

Selinexor in Endometrial Cancer: Key Takeaways

1. **Addressing significant unmet need for maintenance therapy with a growing number of patients**
2. **Well positioned to be the first and only therapy post chemotherapy in the maintenance setting which has the potential to extend time in response and remission**
3. **Top-line Phase 3 data expected early 2022 with rapid sNDA submission**

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ENDOMETRIAL CANCER

Q&A

10 MINUTE BREAK

MYELODYSPLASTIC SYMDROMES

Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
SVP, Sales and Commercial Operations

Guillermo Garcia-Manero, MD
MD Anderson Cancer Center

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

MULTIPLE MYELOMA

~40,000 patients (2L+)[1,5]

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

ENDOMETRIAL CANCER

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

MYELODYSPLASTIC SYNDROMES

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Potential to improve survival in HMA-refractory MDS

MYELOFIBROSIS

~5,000 MF patients[4,5]

Potential to improve patient outcomes in JAKi-refractory MF

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

What is Myelodysplastic Syndrome (MDS)?

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

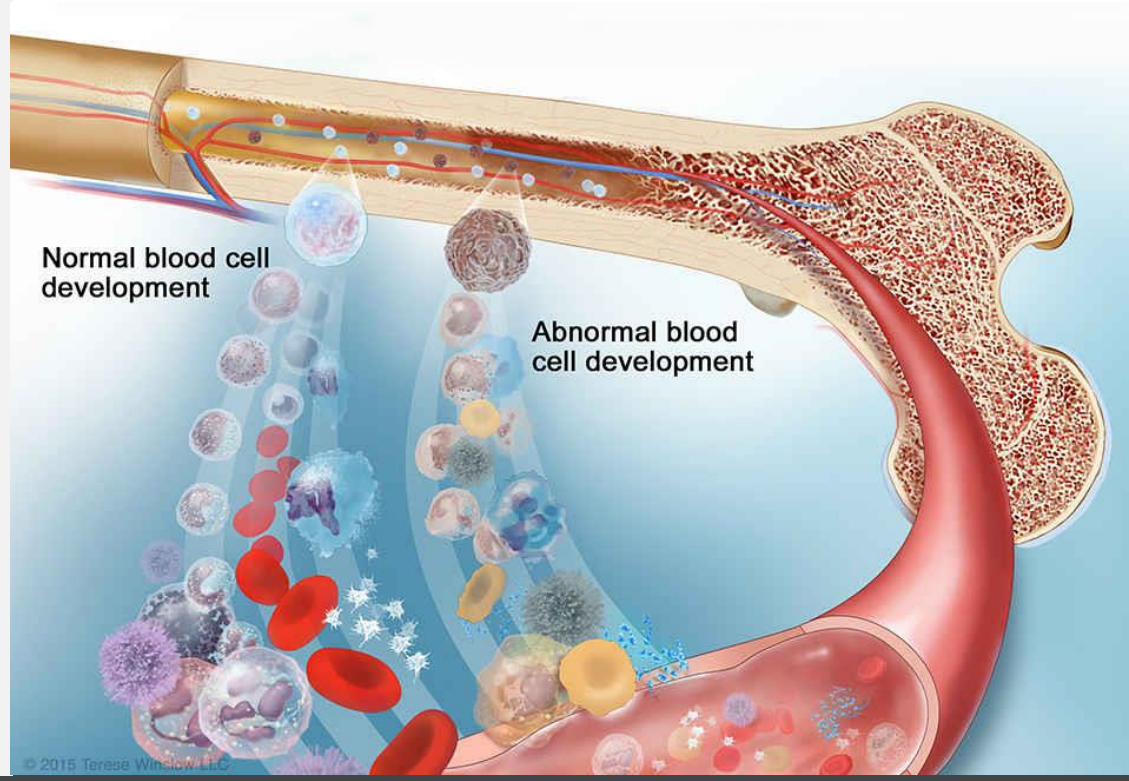
Treatment Landscape

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

Opportunity and Unmet Need

- Prognosis in HMA-refractory disease is poor, with an **expected survival of 4-6 months**[3,4]
- No other class of therapies other than HMA-refractory agents

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



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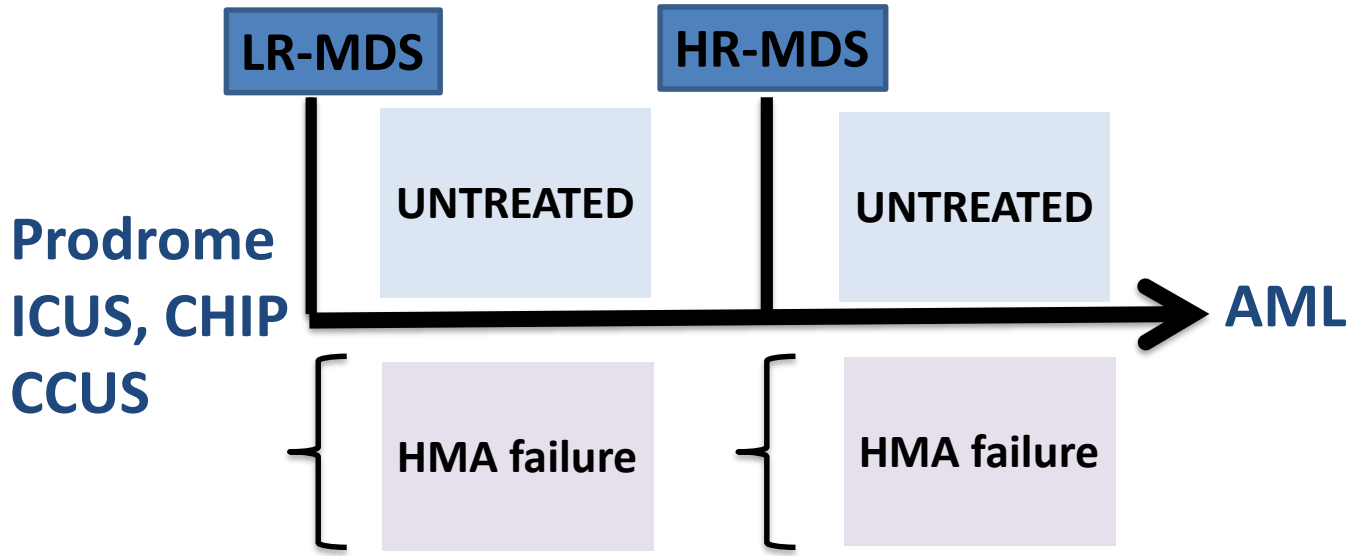
1. Clarivate/DRG Myelodysplastic Syndromes Landscape & Forecast (Nov 2020). **2.** Gil-Perez A. Ther Adv Hematol. 2019 doi:10.1177/2040620719847059.. **3.** Jabbour E, Cancer. 2010;116(16):3830-4. **4.** Prébet T. J Clin Oncol. 2011;29:3322-7. **5.** Clarivate/DRG Myelodysplastic Syndromes Landscape & Forecast (Nov 2020).

HMA Failure MDS

Guillermo Garcia-Manero MD
Professor of Medicine
Chief Section of MDS
Deputy Chair
Department of Leukemia
MD Anderson Cancer Center
University of Texas
Houston, TX

Subsets of patients with MDS based on expected outcome



HMA lower risk failure survival: 14-17 months
HMA higher risk failure survival: 4-6 months

Jabbour. Cancer 2015; Jabbour. Cancer 2010; Steensma Blood 2015.

Definition

- **HMA failure is defined by US FDA:**

  -no response after 4 to 6 cycles of HMA

  -frank progression after 1 cycle of therapy

Questions: HMA failure

- Need to understand pathogenesis
- Need for new targets
- More clinical trials and interventions

Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib vs Best Supportive Care in Patients with Higher-risk Myelodysplastic Syndrome After Failure of Hypomethylating Agents (ONTIME Trial of ON 01910)

G. Garcia-Manero, P. Fenaux, A. Al-Kali, M. R. Baer, M. Sekeres, G. Roboz, G. Gaidano, B. Scott, P. Greenberg, U. Platzbecker, D. P. Steensma, S. Kambhampati, L. Godley, R. Collins, E. Atallah, F. Wilhelm, I. Darnis-Wilhelm, N. Azarnia, M. Maniar, L. R. Silverman, for the ONTIME Investigators

Garcia-Manero et al. Lancet Oncology 2016

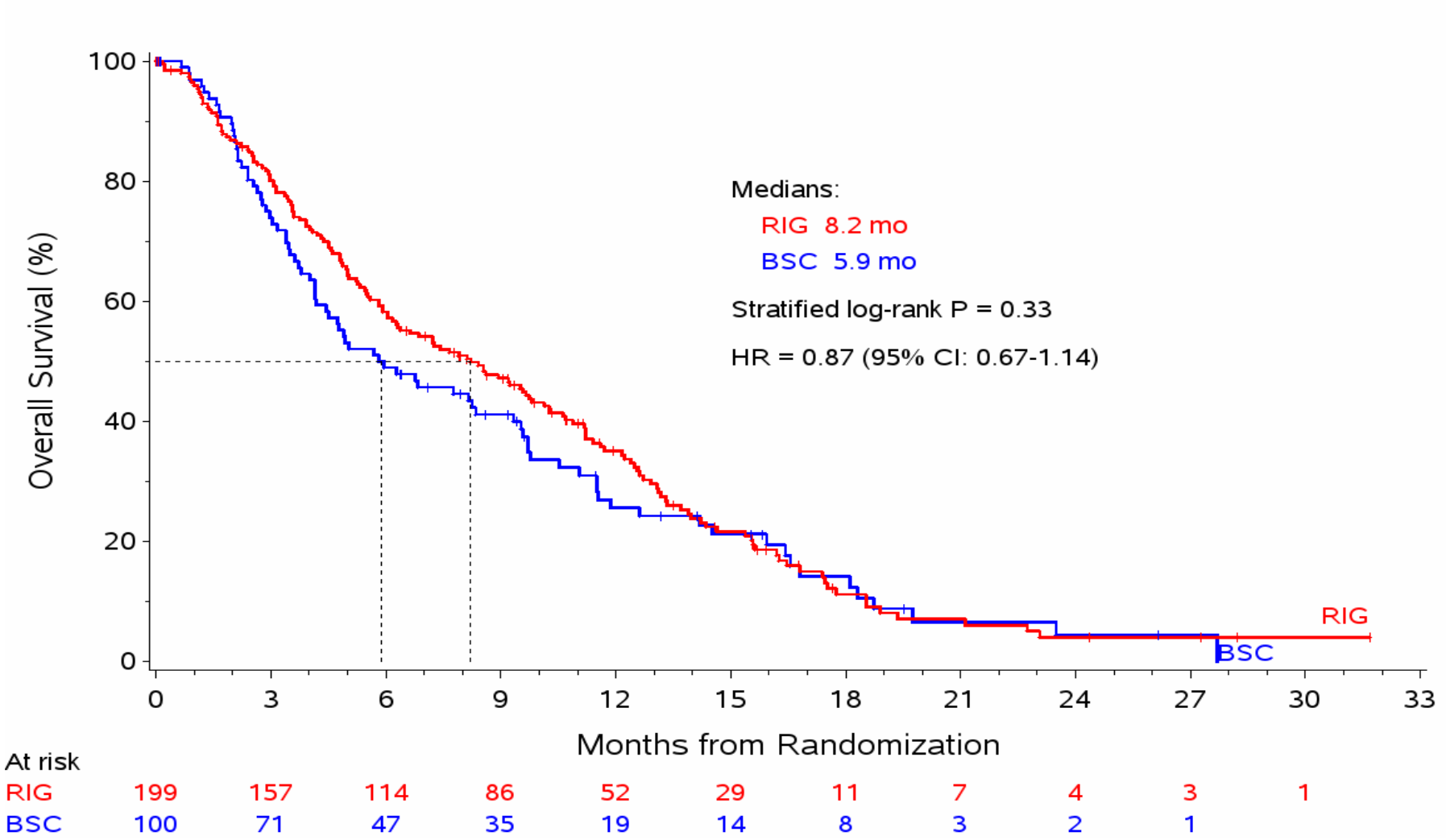
ONTIME Trial: Primary Efficacy Results - ITT

	Rigosertib N = 199	BSC N = 100
Number (%) of deaths	161 (81%)	81 (81%)
Median follow-up (months)	17.6	19.5
Median survival (months)	8.2	5.9
95% CI	6.0 - 10.1	4.1 - 9.3
Stratified HR (rigosertib/BSC)	0.87	
95% CI	0.67 - 1.14	
Stratified log-rank p-value*	0.33	

* Stratification factor: bone marrow blast at randomization (5-19% versus 20-30%)

Garcia-Manero et al. Lancet Oncology 2016

ONTIME Trial: Primary Efficacy Results – ITT



Garcia-Manero et al. Lancet Oncology 2016

ONTIME Trial: ITT Subgroups Correlated with Better Survival Benefit - ITT

Subgroup	Rigosertib		BSC		HR (95% CI)	p-value
	N	Median (mos)	N	Median (mos)		
Monosomy 7	16	5.6	13	2.8	0.24 (0.09-0.66)	0.003
Trisomy 8	22	9.5	8	4.5	0.34 (0.12-0.95)	0.035
Del 7q	17	5.0	3	2.7	0.38 (0.10-1.48)	0.14
Very high risk per IPSS-R	93	7.6	41	3.2	0.56 (0.37-0.84)	0.005

Garcia-Manero. Lancet Oncology 2016

A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax as Monotherapy or in Combination with Azacitidine for the Treatment of Relapsed/Refractory Myelodysplastic Syndrome

565

Amer M. Zeidan[1], Daniel A Pollyea[2], Jacqueline S Garcia[3], Andrew M Brunner[4], Fernando Roncolato[5], Uma Borate[6], Olatoyosi Odenike[7], Ashish Bajel[8], Anne Marie Watson[9], Katharina Götze[10], Florian Nolte[11], Peter Tan[12], Haifa K Al-Ali[13], Wan-Jen Hong[14], Ying Zhou[15], Lori Gressick[15], William Ainsworth[15], Jason Harb[15], Ahmed H Salem[15], John Hayslip[15], Ronan Swords[15]

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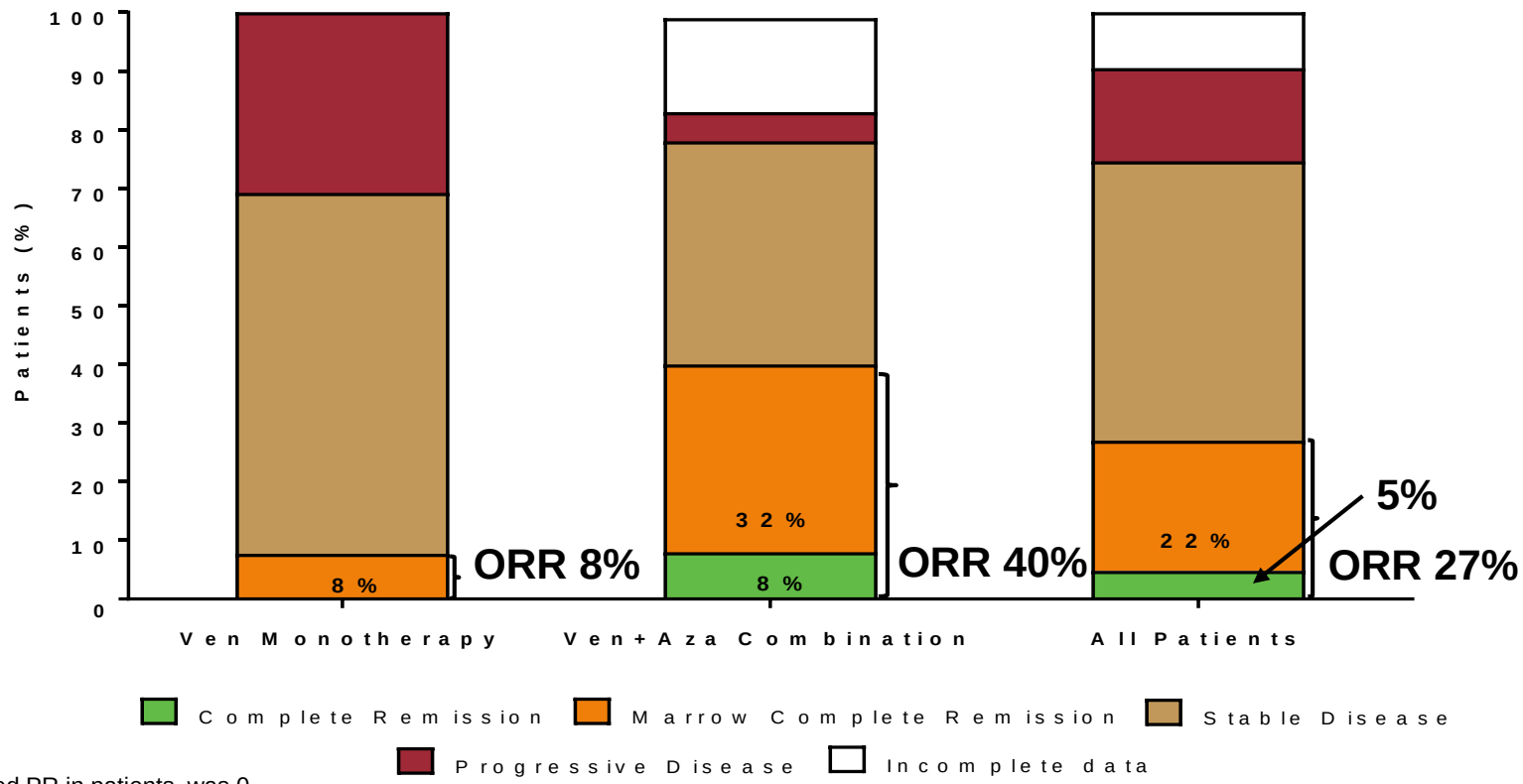
American Society of Hematology (ASH) – 61th Annual Meeting
Orlando, FL, USA ● December 9, 2019

Venetoclax: Overall Response Rates

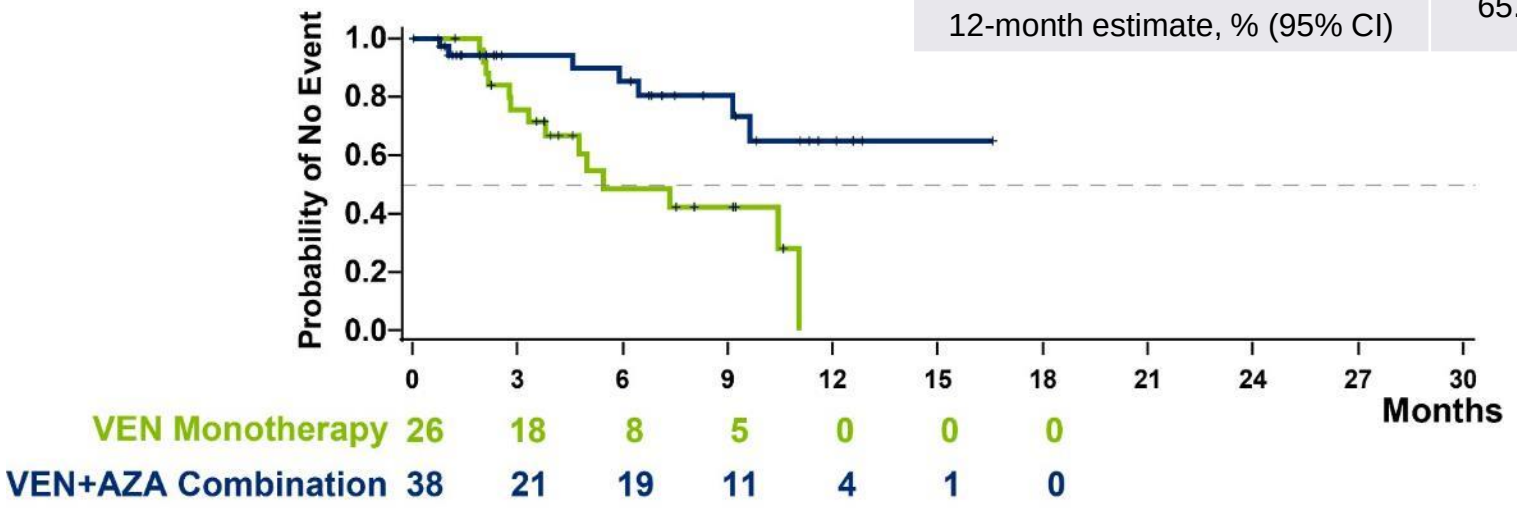


Note: Observed PR in patients was 0
Ven Monotherapy: Ven 400 mg or 800 mg; Ven+Aza Combination: Ven doses 100, 200, or 400 mg + Aza 75 mg/m^2

Data cutoff: 30 AUG 2019

Venetoclax: Overall Survival

Overall survival	
Ven Monotherapy median, months (95% CI)	5.5 (3.3 – 11.1)
Ven+Aza Combination* 12-month estimate, % (95% CI)	65.0 (37.3 – 82.8)



*median OS not reached for Ven+Aza combination therapy
Ven Monotherapy: Ven 400 mg or 800 mg; Ven+Aza Combination: Ven doses 100, 200, or 400 mg+Aza 75 mg/m^2

Data cutoff: 30 AUG 2019

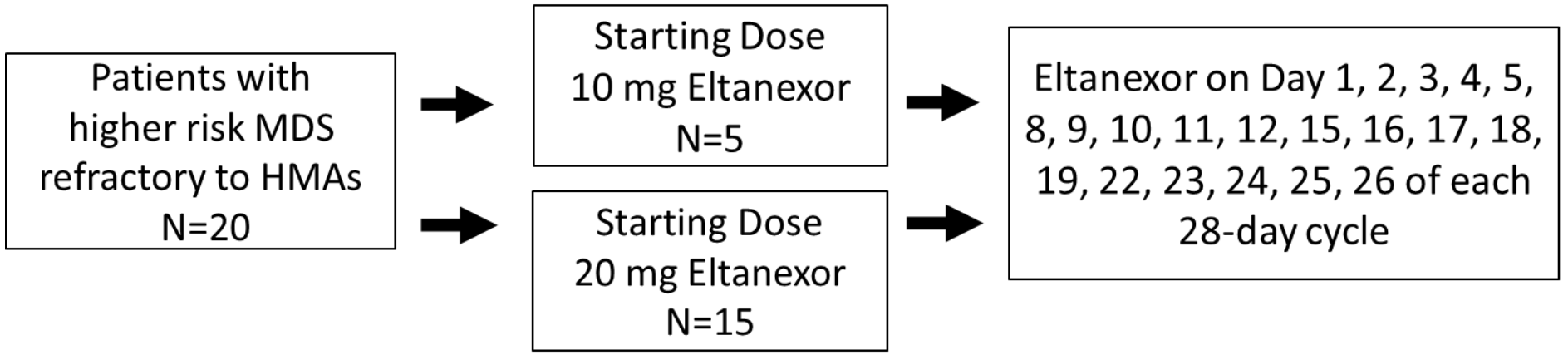
Updated Overall Survival of Eltanexor for the Treatment of Patients With Hypomethylating Agent Refractory Myelodysplastic Syndrome

Sangmin Lee, MD1; Sanjay Ram Mohan, MD, MSCI2; Jessica Knupp, MPH3; Kamal Chamoun, MD3; Xiang Bai, MD, PhD3; Xiwen Ma, PhD3; Jatin Shah, MD3; Michael Kauffman, MD, PhD3; Sharon Shacham, PhD, MBA3; Bhavana Bhatnagar, DO4

1 Division of Hematology and Oncology, Weill Cornell Medicine, New York, NY; 2 Division of Hematology and Oncology, Vanderbilt University Medical Center, Nashville, TN; 3 Karyopharm Therapeutics Inc, Newton, MA; 4 West Virginia University Cancer Institute, Morgantown, WV

EHA 2021

Study Design and Schema



- Phase 1/2 open-label study of the safety, tolerability, and efficacy of eltanexor in multiple myeloma, colorectal cancer, metastatic castrate resistant prostate cancer, and higher risk MDS (NCT02649790)
- In the MDS cohort, patients must have documented diagnosis of progressing MDS with 5%-19% myeloblasts
- Patients should have intermediate-2 or high-risk MDS by International Prognostic Scoring System (IPSS)

EHA 2021

Demographics

Characteristic	Total N=20
Age	
Years: Median (range)	77 (62 - 89)
HMA Refractory	
Primary	20 (100%)
Secondary	0
IPSS Risk Score	
Intermediate-1	1 (5%)
Intermediate-2	7 (35%)
High	12 (60%)
MDACC Risk Score	
Intermediate-1	2 (10%)
Intermediate-2	13 (65%)
High	5 (25%)
MDS Subtype	
De Novo	16 (80%)
Secondary	4 (20%)
Prior Therapies	
Median (range)	2 (1 - 4)
Azacitidine	14 (70%)
Decitabine/ASTX727	11 (55%)

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

	Eltanexor (10mg) N=5	Eltanexor (20mg) N=10	Total N=15
ORR (mCR + HI), N (%)	3 (60)	5 (50)	8 (53.3)
mCR, N (%)	3 (60)	4 (40)	7 (46.7)
HI (with and without mCR), N (%)	1 (20)	3 (30)	4 (26.7)
SD, N (%)	2 (40)	2 (20)	4 (26.7)
PD, N (%)	0	3 (30)	3 (20)
Treatment Duration (Weeks)	15	12.5	13
Median Time to Response (weeks)	8.1	9.1	8.4
Median Duration of Response (95% CI) (weeks)	1.81 (NA, NA)	5.82 (3.02, NA)	4.42

HI = hematologic improvement (minimum of 8 weeks); mCR = marrow complete remission; NA = not available; ORR= overall response rate including CR, PR, mCR and HI; PD = progressive disease; PR = partial response; SD = stable disease

- In the 10-mg cohort (n=5), all patients derived clinical benefit: 3 patients (60%) reached mCR and 2 patients (40%) SD.
- In the 20-mg cohort (n=10), 4 patients (40%) reached mCR and 2 (20%) SD.
- Four patients had HI and became transfusion independent for at least 8 weeks, including 2 patients with tri-lineage HI.

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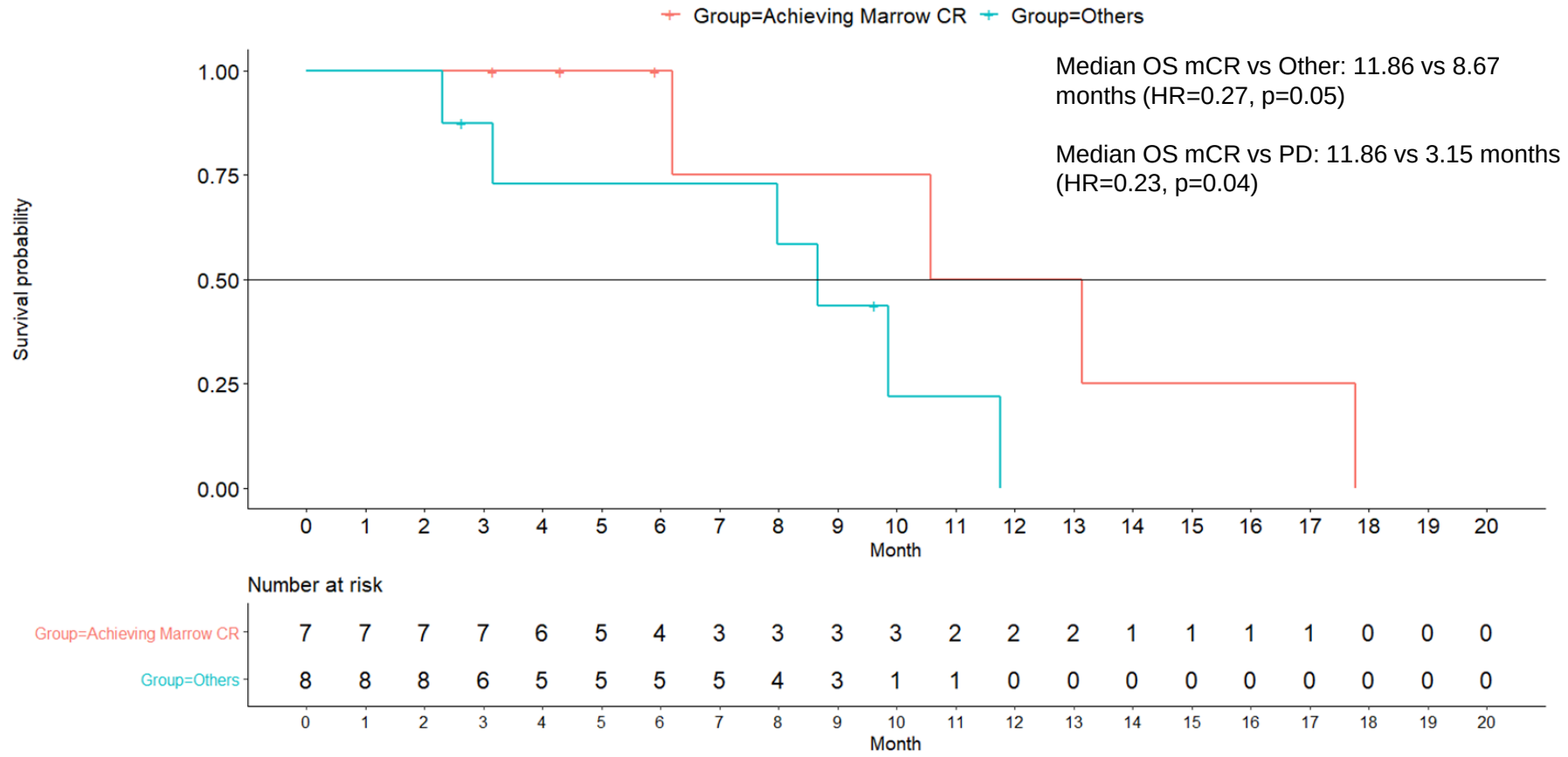
Eltanexor Overall Survival in HMA Refractory MDS> 10 Months



	All patients	mCR (n=7)	HI (n=4)	SD (n=4)	PD (n=3)
Median OS (months)	9.86	11.86	10.58	9.86	3.15

EHA 2021

Conclusions

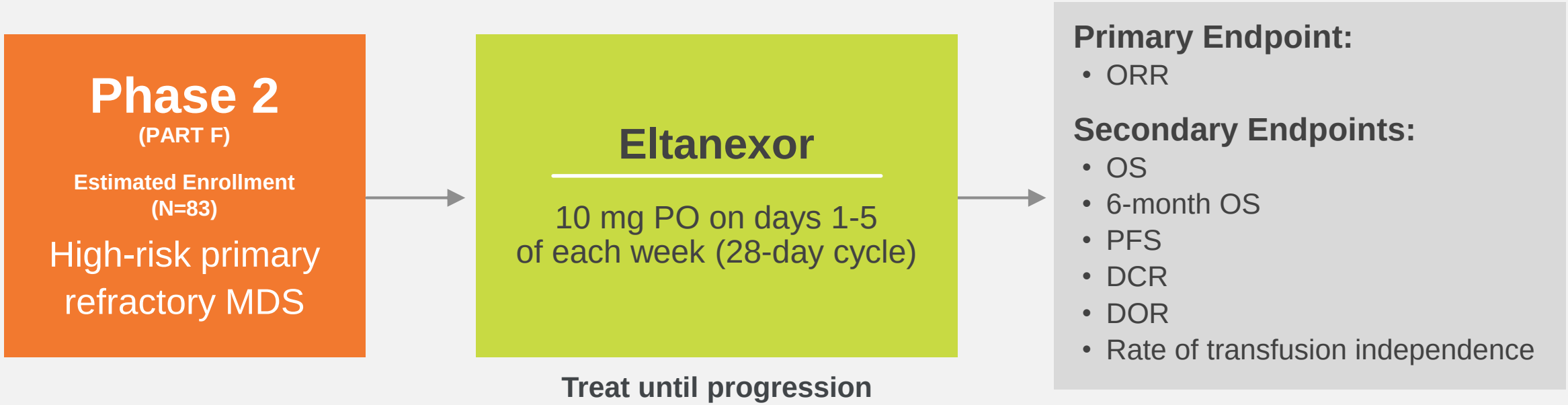
- HMA refractory MDS need new approaches
- Major unmet need
- No good standard of care
- Single-agent oral eltanexor was active in patients with high-risk MDS that is primary refractory to HMAs
- Patients with mCR had significantly longer mOS than patients without mCR or with PD
- Further evaluation of eltanexor in MDS as a single agent and in combination with other agents is warranted

MYELODYSPLASTIC SYNDROMES COMMERCIAL OPPORTUNITY AND WRAP UP

Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
SVP, Sales and Commercial Operations

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



First patient dosed Sept 2021

Top-line data expected 1H 2023

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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.

Eltanexor has the Potential to Improve Survival in HMA-Refractory MDS

Growing Market Opportunity

- Incidence expected to significantly increase due to an aging population and improving disease awareness[1]
- Availability of new options will increase the treatment rate for both higher- and lower-risk MDS patients
- ~15,000 patients diagnosed with intermediate-to-high risk MDS each year in the US[2]
- Prevalence of 60,000 to 170,000 in the US[3]

Competitively Well-positioned

- No agents approved for primary HMA-refractory MDS and need for a class switch post-HMA
- Ongoing agents in development externally are focused in newly diagnosed MDS

Critical Success Factors

- Continue with rapid enrollment to deliver clinically meaningful efficacy in HMA-refractory MDS
- Develop and deepen relationships with key MDS investigators, educating on SINE technology
- Educating on the benefit of a class switch following progression on or intolerance to HMAs
- Leverage internal capabilities

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

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1. Ma, Xiaomei. Epidemiology of Myelodysplastic Syndromes. Am J Med. 2012 Jul; 125(7 Suppl): S2–S5.
2. Clarivate/DRG Myelodysplastic Syndromes Landscape & Forecast (Nov 2020). **3.** Cogle, Christopher. Curr Hematol Malig Rep (2015) 10:272-281.

Eltanexor in MDS: Key Takeaways

1. **Addressing significant unmet need for patients with HMA-refractory MDS**
2. **Single-agent eltanexor showing robust responses and survival in HMA-refractory MDS with the potential to be the first approved new class of therapy**
3. **Exploring combination with HMAs in frontline MDS**

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MYELODYSPLASTIC SYNDROMES

Q&A

MYELOFIBROSIS

Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
SVP, Sales and Commercial Operations

Srinivas Tantravahi, MBBS, MRCP
University of Utah

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

MULTIPLE MYELOMA

~40,000 patients (2L+)[1,5]

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

ENDOMETRIAL CANCER

~14,000 frontline patients[2,5]

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

MYELODYSPLASTIC SYNDROMES

~15,000 intermediate to high-risk patients[3,5]

Potential to improve survival in HMA-refractory MDS

MYELOFIBROSIS

~5,000 MF patients[4,5]

Potential to improve patient outcomes in JAKi-refractory MF

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1. Kantar Cancer Impact. **2.** Sorbe, B et al. Int J Gynecol Cancer 2008. **3.** Clarivate/DRG Epidemiology Data. **4.** https://my.clevelandclinic.org/health/diseases/15672-myelofibrosis. **5.** Annual U.S. incidence.

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

What is Myelofibrosis (MF)?

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

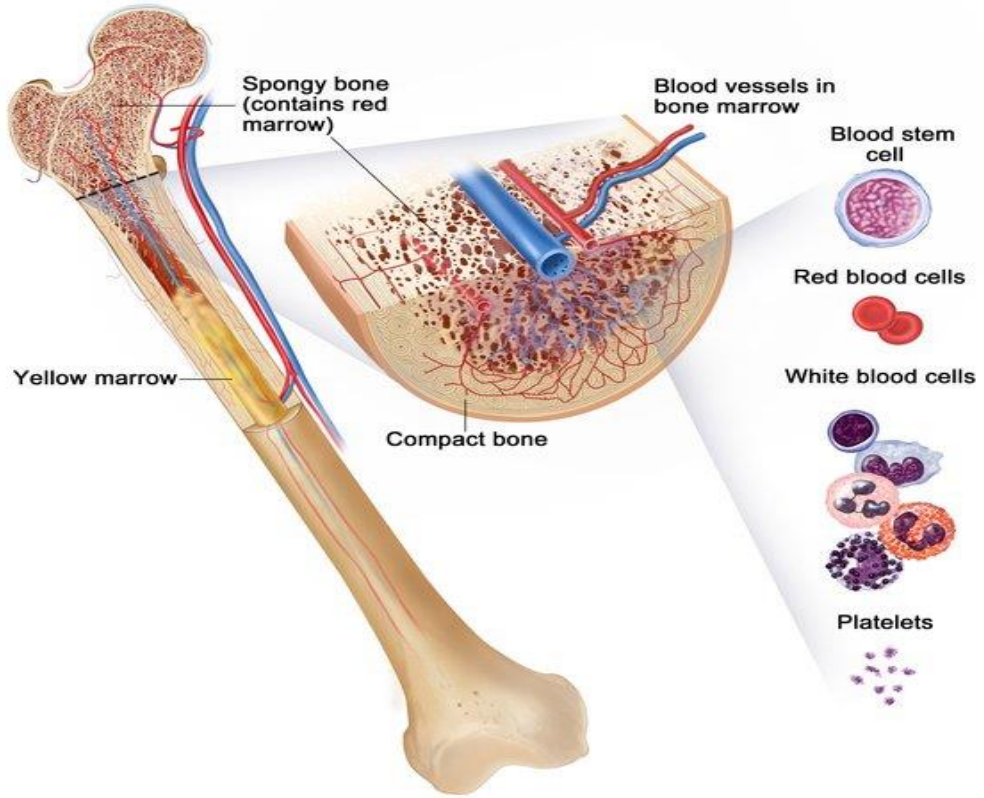
Treatment Landscape

- Ruxolitinib is the standard of care for patients with newly diagnosed MF and it has resulted in splenic and clinical responses up to 4 years for primary responders
- Approximately 40% of patients respond[2]

Opportunity and Unmet Need

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

It is estimated that ~5,000 cases of 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.

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1. https://my.clevelandclinic.org/health/diseases/15672-myelofibrosis. **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.

Selinexor, a potential novel non-JAK inhibitor treatment option for myelofibrosis

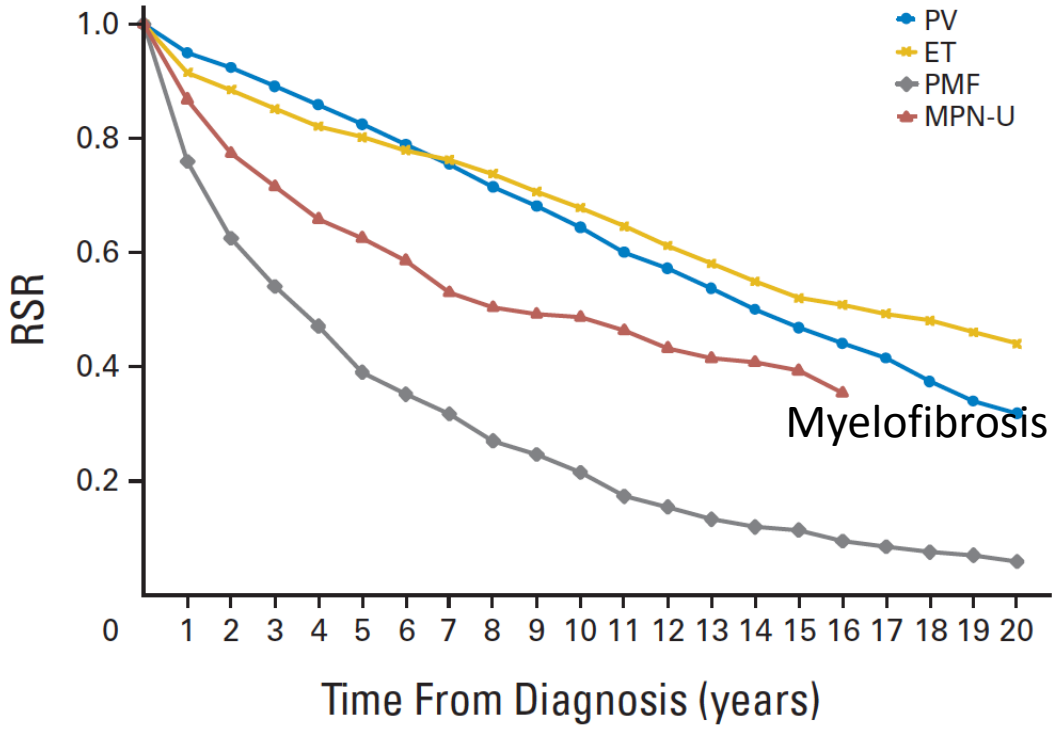
Karyopharm Investors meeting, December 2021

Srinivas Tantravahi, MBBS; MRCP

Huntsman Cancer Institute, University of Utah

Myelofibrosis (MF) is an advanced blood cancer with markedly decreased life expectancy

- The prevalence of MF in the US is 4-6 per 100,000
- Estimated 5-year survival rate in MF patients is 18% (data from US Medicare enrollees)
- Population based study in Sweden also showed worse survival in MF patients compared to other MPNs



1. Price et al. PLoS One. 2014;9(3):e90299
2. Hultcrantz et al. J Clin Oncol. 2012;30:2995-3001.

MF patients experience debilitating symptoms and poor quality of life

Constitutional symptoms (e.g., fatigue, night sweats, fever)

Decreased appetite, weight loss, bone pain

Anemia, low platelet counts, infections

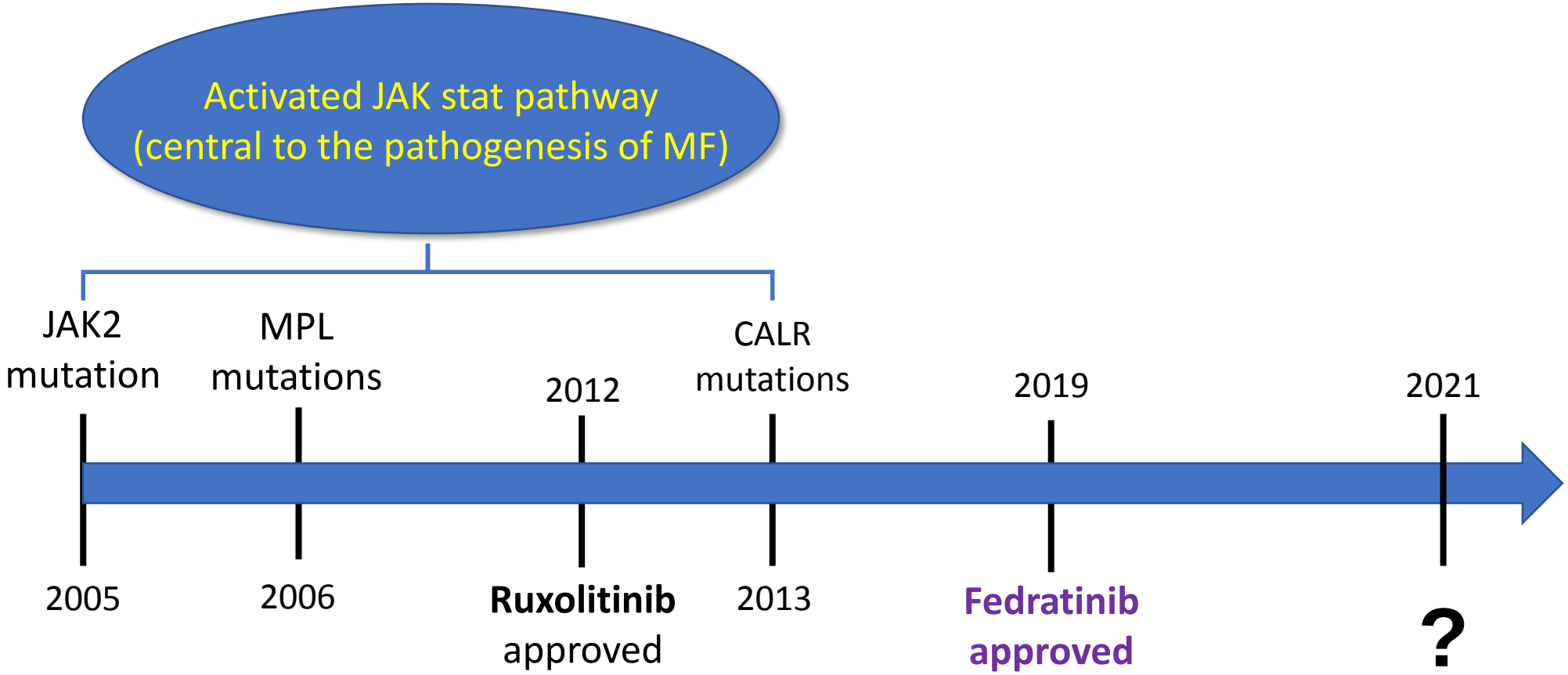
Markedly enlarged spleen causing discomfort and early satiety

Disease related complications: increased risk of blood clots, portal hypertension, pulmonary hypertension

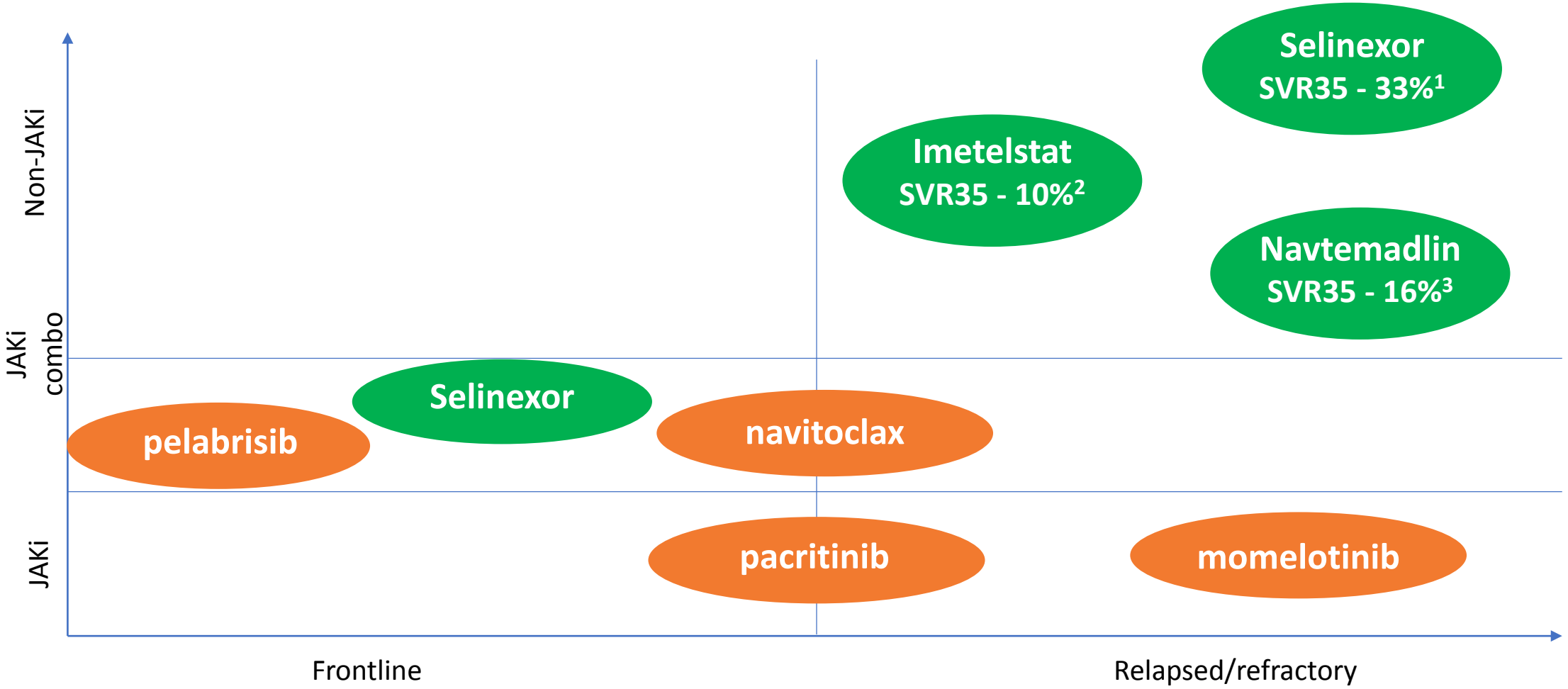
Leukemic progression

1. Mesa et al. BMC Cancer. 2016;16:167.
2. Emanuel et al. J Clin Oncol. 2012;30:4098-4103

Lack of Innovation Over Last Decade for MF with All Approved Agents Being JAKi



Majority of Agents in Development Either JAKi, JAKi Combinations

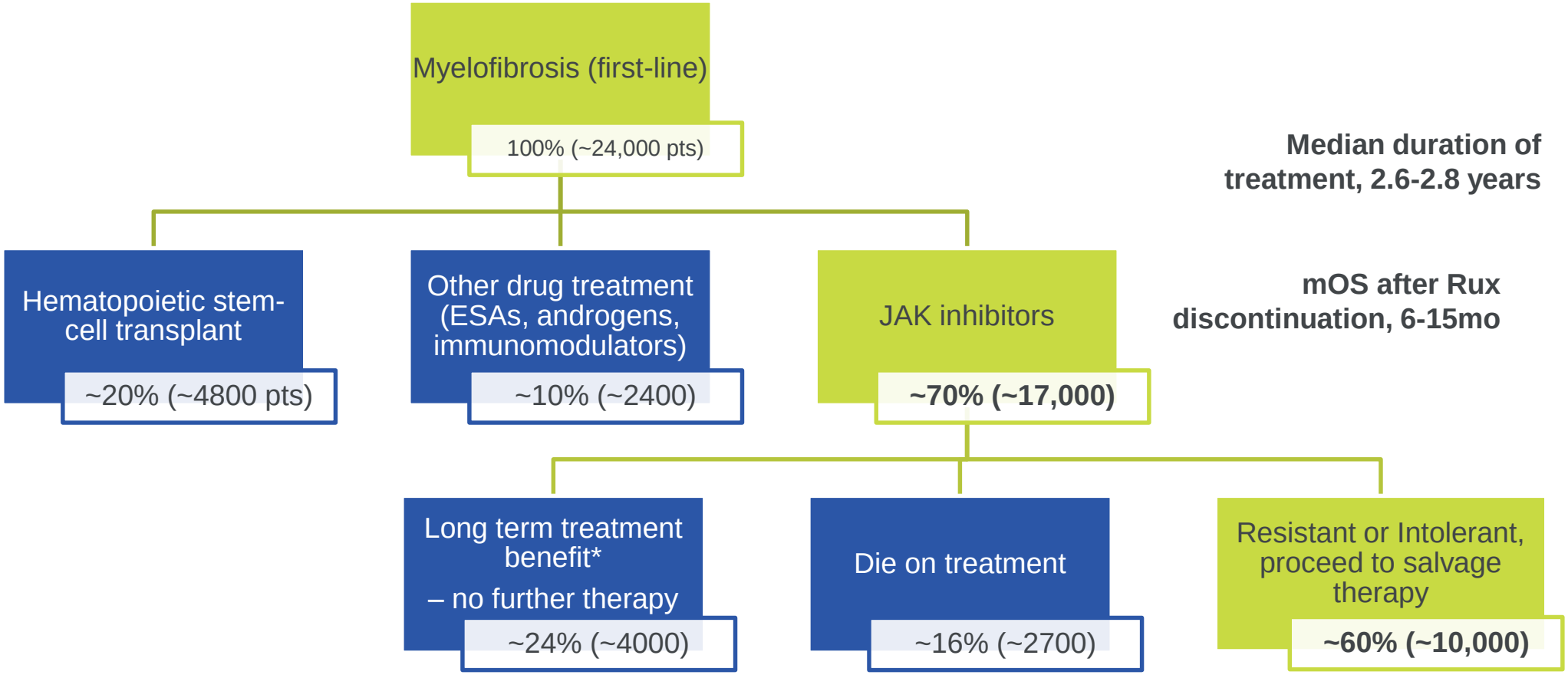


1. Tantravahi, et al. ASH 2021. 2. Mascarenhas, et al. J, Komrokji RS, Palandri F, et al. Randomized, single-blind, multicenter phase II study of two doses of imetelstat in relapsed or refractory myelofibrosis. J Clin Oncol. Published online June 17, 2021. 3. Al-Ali, et al. KRT 232, a first in class, murine double minute 2 inhibitor (MDM2i), for myelofibrosis (MF) relapsed or refractory (R/R) to Janus associated Kinase inhibitor (JAKi) treatment (TX). Oral abstract #S215. 25th EHA Annual Congress; Jun 13, 2020; Virtual.

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

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

Major unmet medical need for patients with MF refractory and/or intolerant to JAK inhibitors: Novel therapeutic approaches are essential



Patients Who Discontinue 1st Line JAK Inhibitors, Myelofibrosis, US+EU5, 2020 estimates

Sources: Fonseca, ASH13; Harrison, 2016; Kuykendall, 2017; Verstovsek, 2017; Decision Resources Myelofibrosis Landscape and Forecast, Oct 2019; Gerds, ASCO20; Harrison, 2020

Nuclear–Cytoplasmic transport (NCT) inhibition is a novel therapeutic target in MF

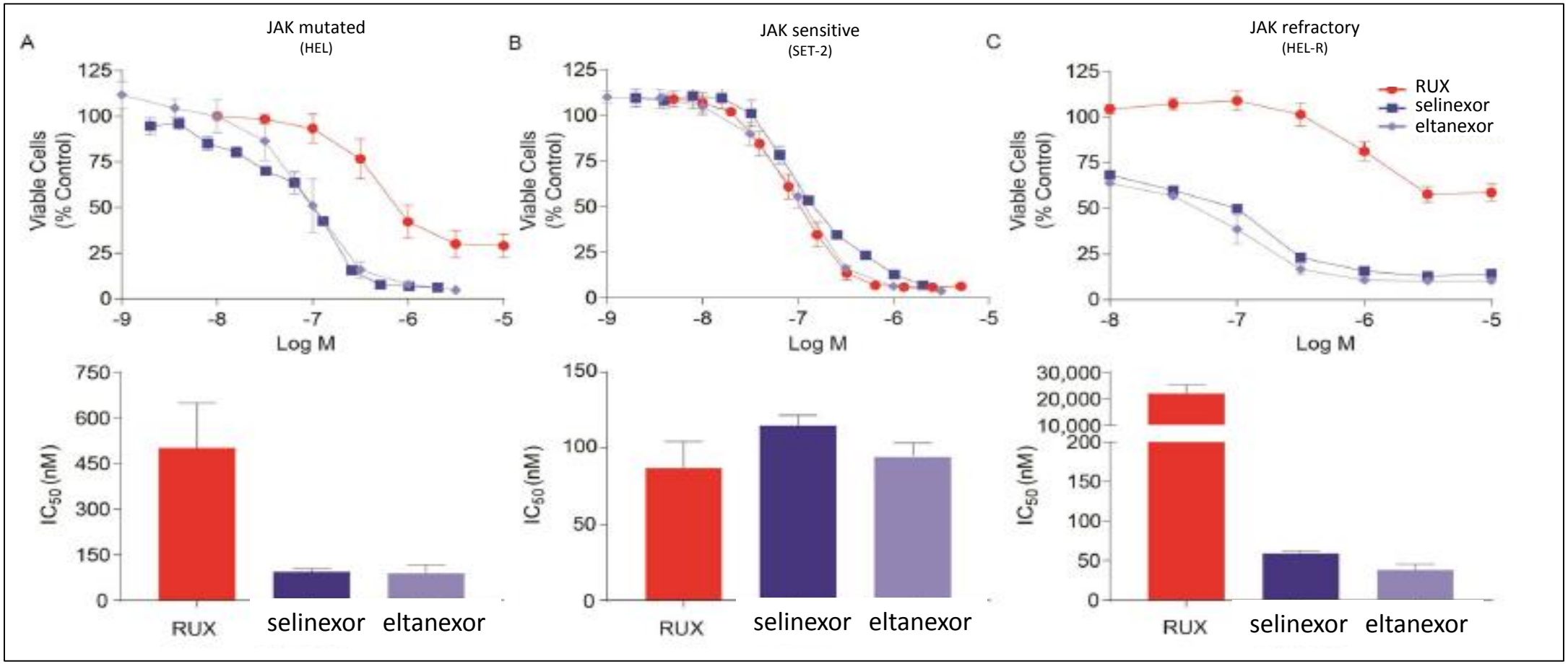
JAK2 mutated HEL and SET-2 cells are exquisitely sensitive to selinexor

Selinexor selectively decreased proliferation and increased apoptosis of patient derived MF cells compared to normal cord blood cells

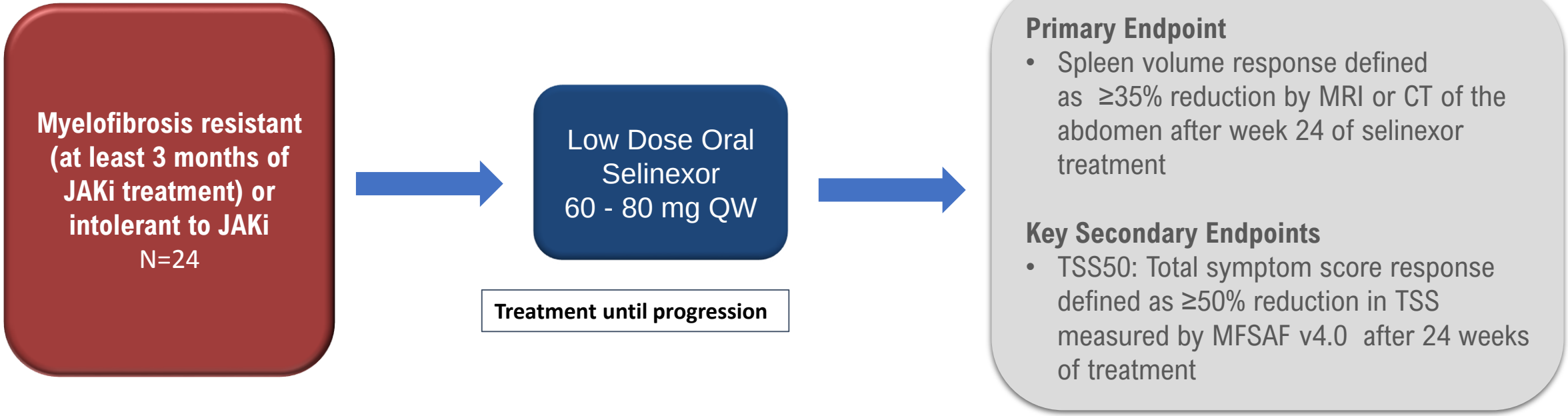
Selinexor showed additive effect with ruxolitinib in growth inhibition and killing of MF cells

Yan et al. Clinc Cancer Res. 2019;25(7):2323-2335.

Preclinical Data Supports Potential for Selinexor in MF[1]



A Phase II Study to Evaluate the Efficacy and Safety of Selinexor in Patients with Myelofibrosis Refractory or Intolerant to JAK1/2 Inhibitors (ESSENTIAL study)



- Bone marrow assessment at screening, week 24
- MRI or CT abdomen at screening and every 12 weeks in 1st year and every 24 weeks in 2nd year
- MPN-SAF TSS at baseline and every 4 weeks
- CBC at screening, QW until week 4, Q 2 weeks until week 24 and then every 4 weeks.

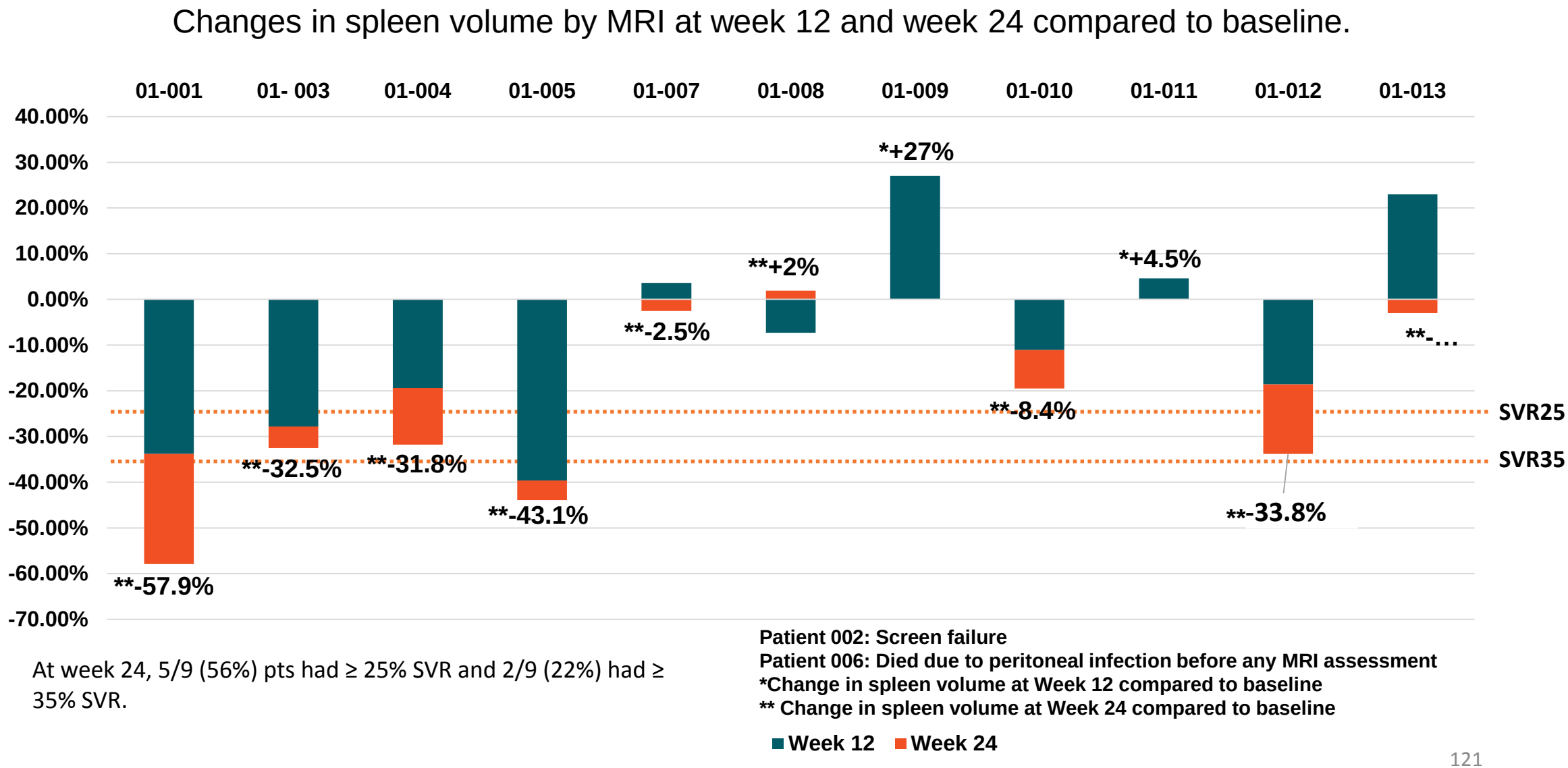
Baseline Demographics: ESSENTIAL study

- 12 patients were treated with selinexor on the study thus far
- Median age was 68 years (range 43 to 80 years)
- Median duration of JAKi therapy was 22 months (range 0.5 to 96 months)
- 92% (11 pts) had MF resistant to prior JAKi
- 67% (8 pts) had at least one high risk molecular mutation

Oral Abstract, Session 634, 2021 American Society of Hematology, December 2021, Atlanta, USA

Single-agent selinexor resulted in sustained spleen responses in refractory MF patients

In patients who had ≥24 weeks of selinexor, SVR35 occurred in 3 of 9 (33%) at any point during study



At week 24, 5/9 (56%) pts had ≥ 25% SVR and 2/9 (22%) had ≥ 35% SVR.

Oral Abstract, Session 634, 2021 American Society of Hematology, December 2021, Atlanta, USA

Selinexor demonstrated efficacy in addition to SVR35 with improvement in transfusion dependency and anemia

Spleen responses improved over time on selinexor treatment in MF patients who progressed on or intolerant to JAKi (median duration of prior JAKi = 22 months)

Of the two patients that were red cell transfusion dependent at baseline, 1 became transfusion independent after 36 weeks of treatment (114 weeks)

Hb improvement was also observed in transfusion independent patients with Hb <10 g/dL

Oral Abstract, Session 634, 2021 American Society of Hematology, December 2021, Atlanta, USA

Safety of Selinexor on ESSENTIAL Study

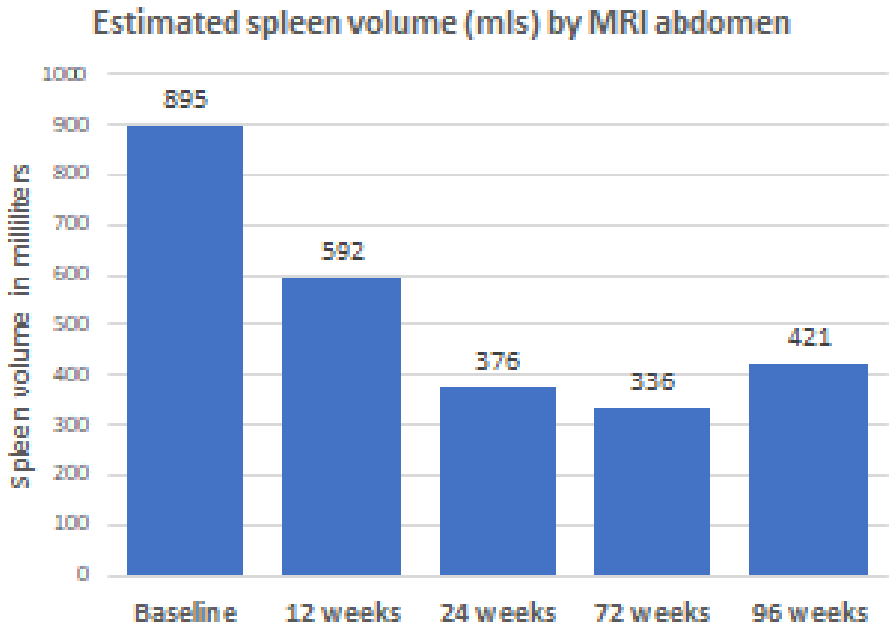
- The most common treatment related adverse event was weight loss (grade 2 in 4 pts and grade 3 in 1 patient)

- Six patients remain on therapy (median 36 weeks; range 12 to 114 weeks)
  - 2 patients discontinued due to side effects

Oral Abstract, Session 634, 2021 American Society of Hematology, December 2021, Atlanta, USA

Case Study to illustrate durable spleen and hemoglobin response on selinexor

- 76-year-old woman with *JAK2*V617F positive primary myelofibrosis
- Prior treatment include ruxolitinib; and ruxolitinib + azacytidine combination therapy
- Baseline PRBC transfusion dependent anemia and thrombocytopenia
- Started on single agent selinexor 80 mg weekly and the dose decreased to 60 mg weekly at week 4
  - Week 24 MRI showed 57.9% reduction spleen volume compared to baseline
  - Became transfusion independent after 36 weeks of treatment and remains on study treatment at data cut off (114 weeks)
  - WBC count normalized after 1 week and sustained decrease in LDH level to normal range
- Side effects included thrombocytopenia and weight loss



- **Best spleen response: 62.5% reduction in spleen volume compared to baseline**
- **Week 24 showed 57.9% reduction in spleen volume compared to baseline**

Final Remarks

- Huge unmet need for novel treatment options for MF patients after failure of JAK inhibitor treatment
- In ESSENTIAL study Selinexor has shown preliminary single agent activity of 33% with sustained spleen responses in MF patients refractory to JAKi
- Selinexor has been well tolerated in MF patients in ESSENTIAL study for up to 2 years
- Phase 2 study currently underway in JAKi previously treated MF patients
  - Phase 1 also ongoing in combo with ruxolitinib in JAKi naïve patients
- Future combination studies of selinexor with navitoclax (BCL-2 inhibitor) and pelabrisib (BET inhibitor) should be considered

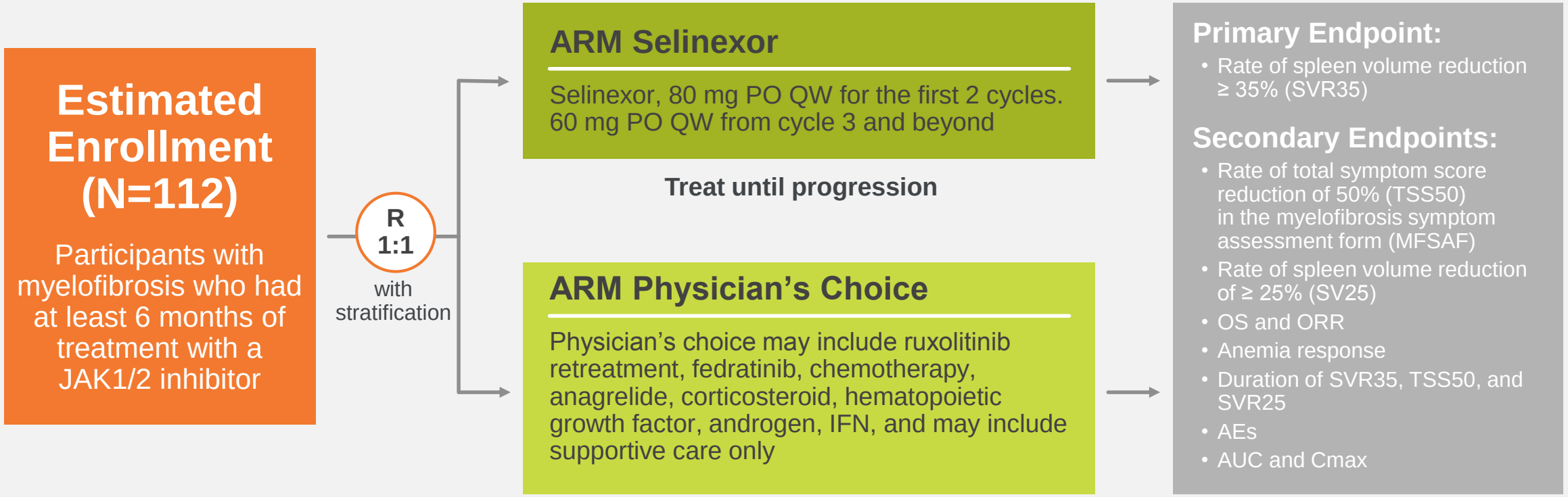
Updated Data from ESSENTIAL Study to be Presented at ASH on December 11, 2021

MYELOFIBROSIS COMMERCIAL OPPORTUNITY AND WRAP UP

Jatin Shah, MD
Chief Medical Officer

Sohanya Cheng
SVP, Sales and Commercial Operations

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



First patient dosed December 2021

Top-line data expected 2H 2023

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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.

Selinexor has the Potential to Improve Patient Outcomes in JAKi-refractory MF

Growing Market Opportunity

- Incidence is expected to significantly increase over the next decade due to aging population and early detection
- ~5,000 myelofibrosis patients in the US[1]
- Prevalence of 16,000-18,500 in the US[2]

Competitively Well-positioned

- No other class of drugs approved in ruxolitinib-refractory MF and need for a class switch post ruxolitinib
- Anemia side effect is a major problem with JAKi agents and limits its use in combinations in relapse setting

Critical Success Factors

- Continue with rapid enrollment to deliver clinically meaningful efficacy in JAKi-refractory MF
- Develop and deepen relationships with key MF investigators, educating on SINE technology
- Educating on the benefit of a class switch following refractory or intolerant to JAKi
- Leverage internal capabilities

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1. https://my.clevelandclinic.org/health/diseases/15672-myelofibrosis.
2. Clarivate/ DRG Myelofibrosis Niche & Rare Disease Landscape & Forecast (Nov 2020).

Selinexor in Myelofibrosis: Key Takeaways

1. **Addressing significant unmet need for patients with JAKi-refractory MF**

2. **Single-agent selinexor showing robust responses in JAKi-refractory MF with the potential to be the first approved new class of therapy**

3. **Exploring combination with JAKi in frontline MF**

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MYELOFIBROSIS Q&A

PARTNERSHIPS, FINANCIAL HIGHLIGHTS AND MILESTONES

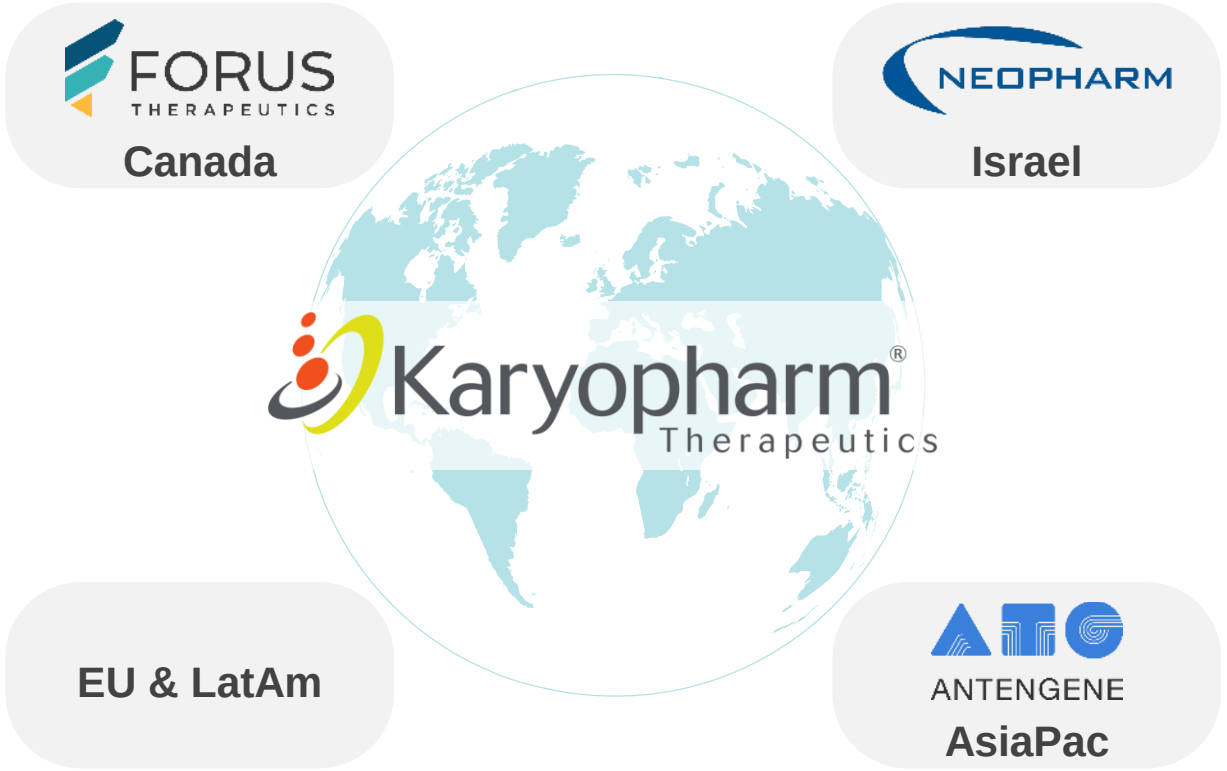
Stephen Mitchener
Chief Business Officer

Michael Mason
Chief Financial Officer

Strategic Partnerships Driving Expansion of Our Global Footprint

Partnerships Serving Key Global Markets

- Ex-US partners continue to strategically advance NEXPOVIO both commercially and in the clinic
- Karyopharm European efforts focused on:
  - Enabling an EMA decision for 2L+ based on BOSTON study[1]
  - Supporting reimbursement opportunity with value dossier preparation



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

Multiple Myeloma: 2nd Line + Patients

Large Ex-US Opportunity to Bring NEXPOVIO to Appropriate Multiple Myeloma Patients

Canada: 3,300[1]

FORUS THERAPEUTICS

LatAm: 12,000[3]

EU: 30,700[2]

APAC: 14,000[4]

ANTENGENE

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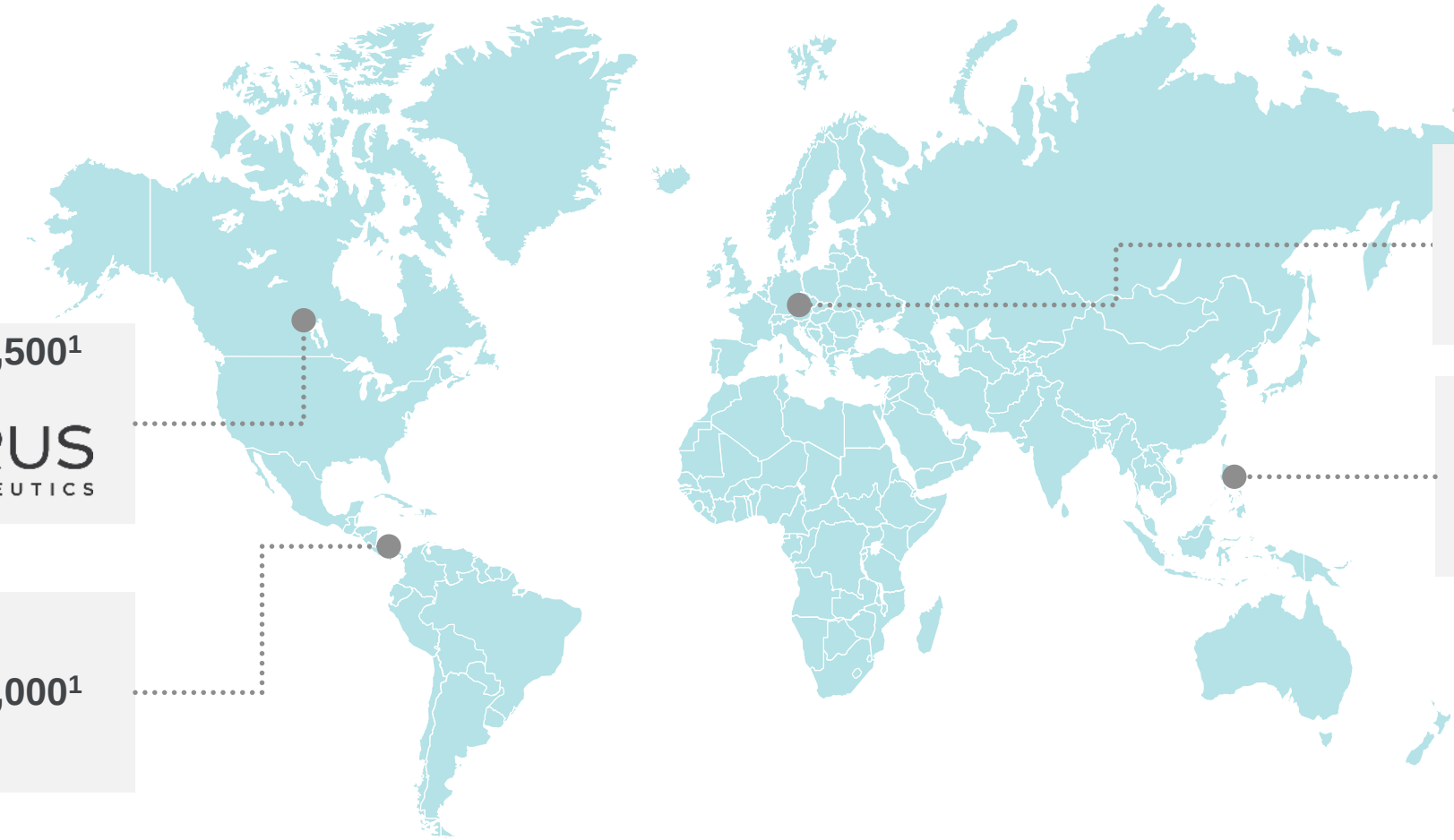
Sources

1. Myeloma Canada **2.** Decision Resource Group **3.** Epic Oncology [4] Extrapolated from Incidence Rate

Endometrial Cancer Patients: Maintenance Eligible

Dynamic Market Growth Expected—Driven by Introduction of Maintenance Therapy



Canada: 2,500[1]

FORUS THERAPEUTICS

LatAm: 11,000[1]

EU: 17,000[1]

APAC: 10,500[1]

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Sources
1. Extrapolated from Decision Resource Group

Financial Snapshot

$209.3M

CASH, EQUIVALENTS & INVESTMENTS
30-Sept-2021

Mid 2023

EXPECTED RUNWAY

$26.7M

Net Product Revenue
3Q 2021

75.5M

SHARES OUTSTANDING
27-Oct-2021

- 2022 R&D expense expected to decrease by ~15% compared to 2021
- Expect to provide 2022 annual product revenue guidance during 1Q 2022
- Deliver on advancing pipeline

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Continued Focus on Delivering Results and Advancing the Pipeline

Milestones 1H 2022

1. Continue to enhance commercial capabilities and increase US XPOVIO sales
2. Dose first patient in Phase 3 study evaluating selinexor + pomalidomide in patients with multiple myeloma
3. Report top-line Phase 3 selinexor SIENDO data
4. Submit sNDA for selinexor in endometrial cancer
5. EMA decision expected in 2L+ based on BOSTON study[1]
6. Commence pre-launch activities for selinexor in endometrial cancer

Milestones 2H 2022 and 2023

1. Continue to enhance commercial capabilities and increase US XPOVIO sales
2. Potential approval and launch of selinexor as a maintenance therapy in endometrial cancer
3. Realize further milestones and royalties from approvals and sales in ex-US territories
4. Report top-line Phase 2 eltanexor data in MDS (1H 2023)
5. Report top-line Phase 2 selinexor data in MF (2H 2023)
6. Complete enrollment in Phase 3 study evaluating selinexor + pomalidomide in MM (2H 2023)

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Two Novel SINE Agents Driving Growth as We Build Upon Four Core Areas

Opportunity to expand into additional lines of therapy in all four core indications and potential new tumor types

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Final Q&A

Karyopharm® Therapeutics

Thank you!

December 2021