Safety and Efficacy of the Combination of Selinexor, Lenalidomide and Dexamethasone (SRd) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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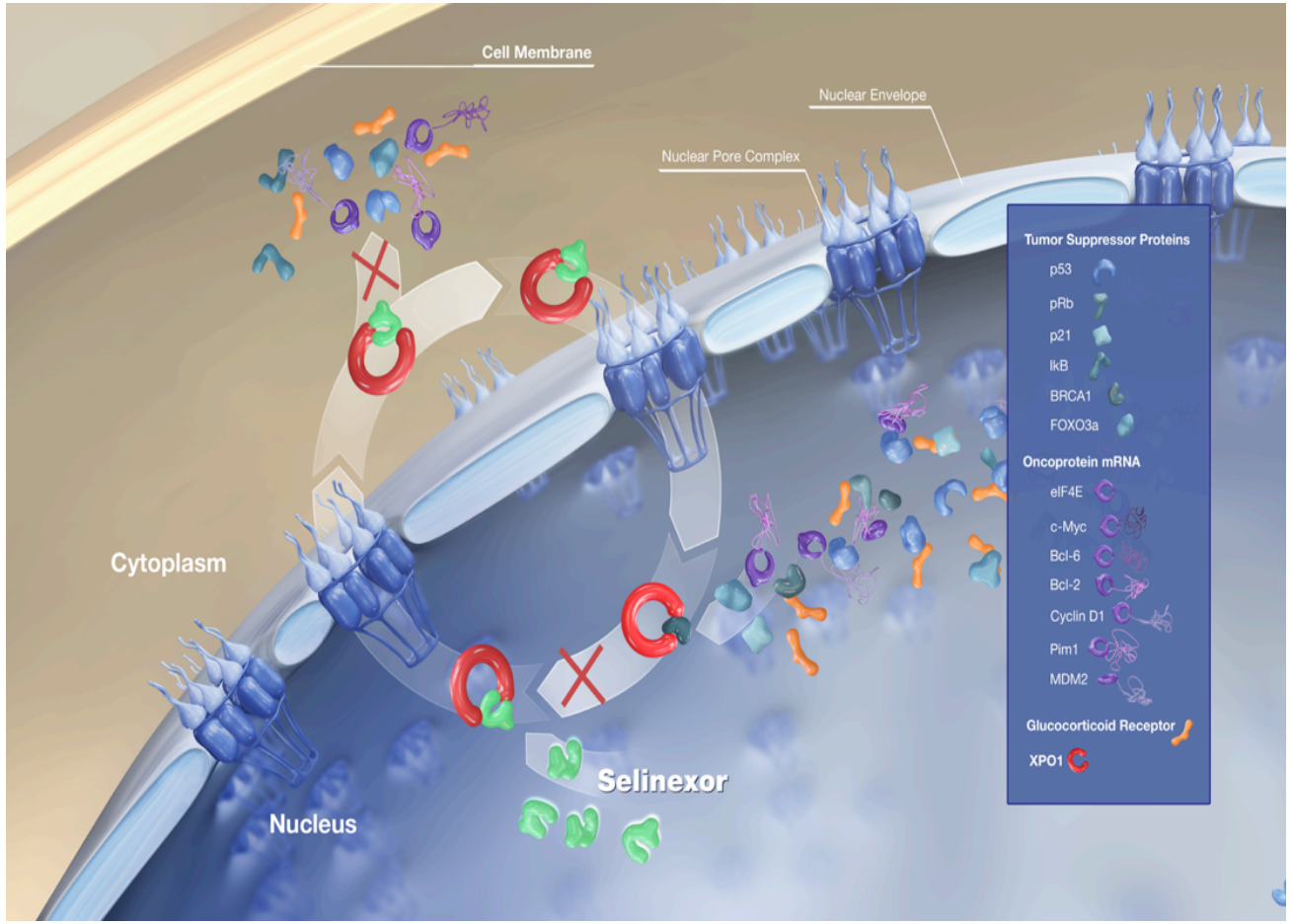
Selinexor:

First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-4]



Exportin 1 (XPO1) is the major nuclear export protein for:

- Tumor suppressor proteins (TSPs, e.g., p53, IκB, and FOXO)
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)
- Glucocorticoid receptor (GR)

XPO1 is overexpressed in MM:

- High **XPO1** levels enable cancer cells to escape TSP-mediated cell cycle arrest and apoptosis
- **XPO1** levels correlate with poor prognosis and drug resistance

Selinexor is an oral selective **XPO1 inhibitor**; preclinical data supports that selinexor:

- Reactivates multiple TSPs by preventing nuclear export
- Inhibits oncoprotein translation
- Reactivates GR signaling in presence of dexamethasone

[1]Schmidt et al., Leukemia, 2013, [2]Tai et al., Leukemia, 2013, [3]Argueta et al., Oncotarget, 2018 [4]Turner et al, 2017 unpublished

Background / Rationale: Selinexor and Lenalidomide Activity in Heavily Treated MM

STORM*: Selinexor + Dexamethasone[1]

Refractory to **Dara, PI**, and **IMiD**

ORR: 26.2%

ORR: 25.3% (Penta-Ref)

PFS: 3.7 months (Overall)

MM-009: Lenalidomide + Dexamethasone[2]

Patients ≥ 1 prior MM therapy

ORR: 61%

PFS: 11.1 months

Selinexor demonstrates synergistic activity in combination with lenalidomide *in vivo*[3]

***Selinexor (+ dex) received accelerated approval from the FDA for patients with RRMM, with ≥4 prior therapy regimens, and whose disease is refractory to at least 2 PIs, 2 IMiDs, and an anti-CD38 MoAb**

[1]*Chari et al., New England Journal of Medicine, 2019*
[2]*Weber et al., New England Journal of Medicine, 2007*
[3]*Carlson et al., ESH 2014*

STOMP Study Design

Primary Objective: Determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D)

Patient Populations:

- **Arm SRd: selinexor + lenalidomide + dexamethasone – Patients who received ≥1 prior lines of therapy for MM**
- Arm SRd-NDMM: selinexor + lenalidomide + dexamethasone in newly diagnosed MM patients
- Arm SPd: selinexor + pomalidomide + dexamethasone
- Arm SVd: selinexor + bortezomib + dexamethasone
- Arm SKd: selinexor + carfilzomib + dexamethasone
- Arm SDd: selinexor + daratumumab + dexamethasone

SRd Dosing Scheme: 3 + 3 design was used for dose escalation phase

Oral Selinexor
60 mg BIW or QW
80 mg QW
28 day cycle

+

Oral Lenalidomide
25 mg QD
Daily, 21 day cycle

+

Oral Dexamethasone
20 mg BIW or **40 mg** QW

PO=per oral, BIW=twice-weekly, QW=once-weekly, QD=once daily

Patient Characteristics

Patient Characteristics	N
Enrolled as of August 1, 2019 (Enrollment is complete)	**24**
60 mg selinexor BIW + 25 mg lenalidomide QD	5
80 mg selinexor QW + 25 mg lenalidomide QD	7
60 mg selinexor QW + 25 mg lenalidomide QD (RP2D)	**12**
Median Age, Years (range)	**67** (49 – 84)
Males : Females	**13** (54%) : **11** (46%)
Median Time from Diagnosis to SRd Treatment, Years (range)	4.5 (<1 – 22)
Median Prior Regimens All Patients (range)	**1 (1–8)**
Proteasome Inhibitor (Treated : Refractory)	24 (100%) : 13 (65%)
Lenalidomide (Treated : Refractory : Naïve)	9 (38%) : 5 (21%) : 15 (63%)
Autologous Stem Cell Transplant	12 (50%)
Median Prior Regimens RP2D Patients (range)	**4 (1–8)**
Lenalidomide (Treated : Refractory : Naïve)	5 (42%) : 3 (25%) : 7 (58%)

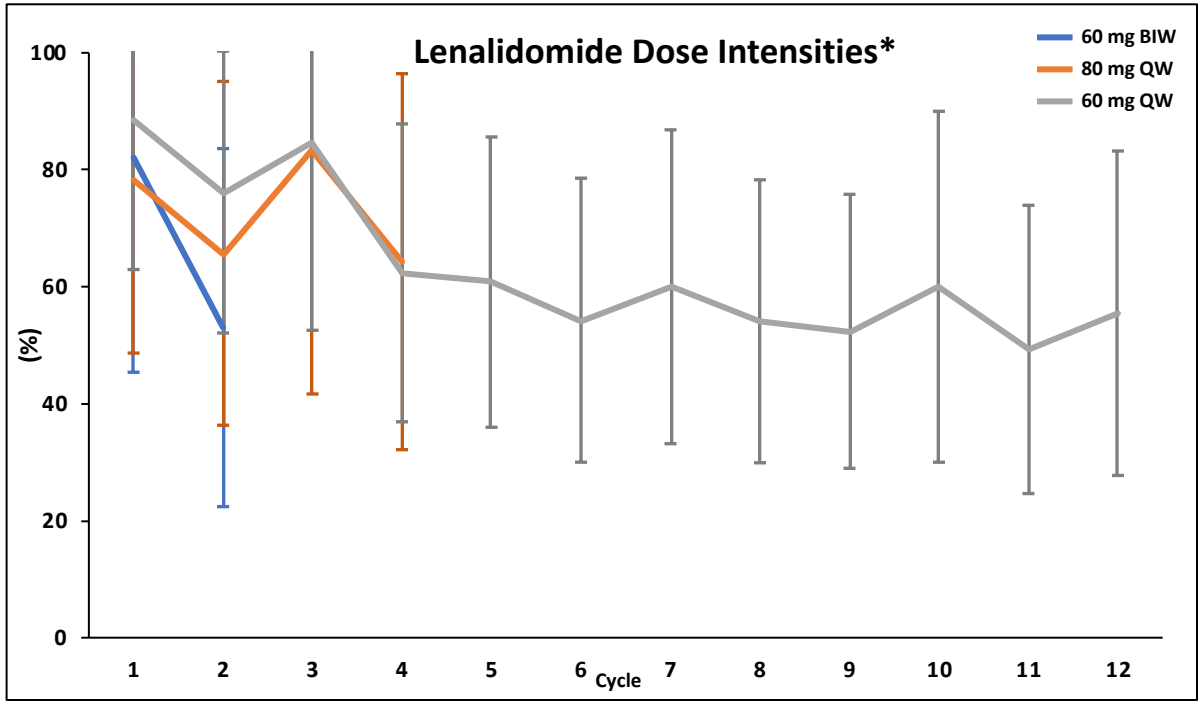
Treatment-Related Adverse Events in ≥10% Patients

AE Term	60 mg BIW, 80 mg QW Sel + 25 mg Len QD (N=12)			60 mg QW Sel + 25 mg Len QD – RP2D (N=12)			Total (N=24)
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**	
Thrombocytopenia	**1 (8.3)**	**2 (16.7)**	**6 (50.0)**	**--**	**3 (25.0)**	**4 (33.3)**	**16 (66.7)**
Neutropenia	**--**	**5 (41.7)**	**2 (16.7)**	**--**	**4 (33.3)**	**4 (33.3)**	**15 (62.5)**
Anemia	3 (25.0)	1 (8.3)	--	1 (8.3)	1 (8.3)	--	**6 (25.0)**
Gastrointestinal							
Nausea	**8 (66.7)**	**--**	**--**	**6 (50.0)**	**1 (8.3)**	**--**	**15 (62.5)**
Anorexia	**5 (41.7)**	**2 (16.7)**	**--**	**5 (41.7)**	**--**	**--**	**12 (50.0)**
Vomiting	**4 (33.3)**	**--**	**--**	**4 (33.3)**	**--**	**--**	**8 (33.3)**
Constipation	5 (41.7)	--	--	1 (8.3)	--	--	**6 (25.0)**
Diarrhea	2 (16.7)	--	--	4 (33.3)	--	--	**6 (25.0)**
Asthenia	1 (8.3)	--	--	2 (16.7)	1 (8.3)	--	**4 (16.7)**
Altered Taste	3 (25.0)	--	--	--	--	--	**3 (12.5)**
Constitutional							
Fatigue	**5 (41.7)**	**2 (16.7)**	**--**	**4 (33.3)**	**2 (16.7)**	**--**	**13 (54.2)**
Weight Loss	**4 (33.3)**	**1 (8.3)**	**--**	**5 (41.7)**	**--**	**--**	**10 (41.7)**
Other							
Dehydration	1 (8.3)	--	--	2 (16.7)	1 (8.3)	--	**4 (16.7)**
Dizziness	2 (16.7)	--	--	2 (16.7)	--	--	**4 (16.7)**
Muscle Spasms	1 (8.3)	--	--	3 (25.0)	--	--	**4 (16.7)**
Vision Blurred	--	1 (8.3)	--	3 (25.0)	--	--	**4 (16.7)**

Safety data cutoff of August 1, 2019

- No treatment-related Grade 5 events were reported

Relative Dose Intensities



- **Prolonged treatment and dosing on selinexor and lenalidomide was seen on 60 mg QW arm (RP2D)**

*Graph depicts cycle points where ≥3 patients' data are available

Dose Limiting Toxicities

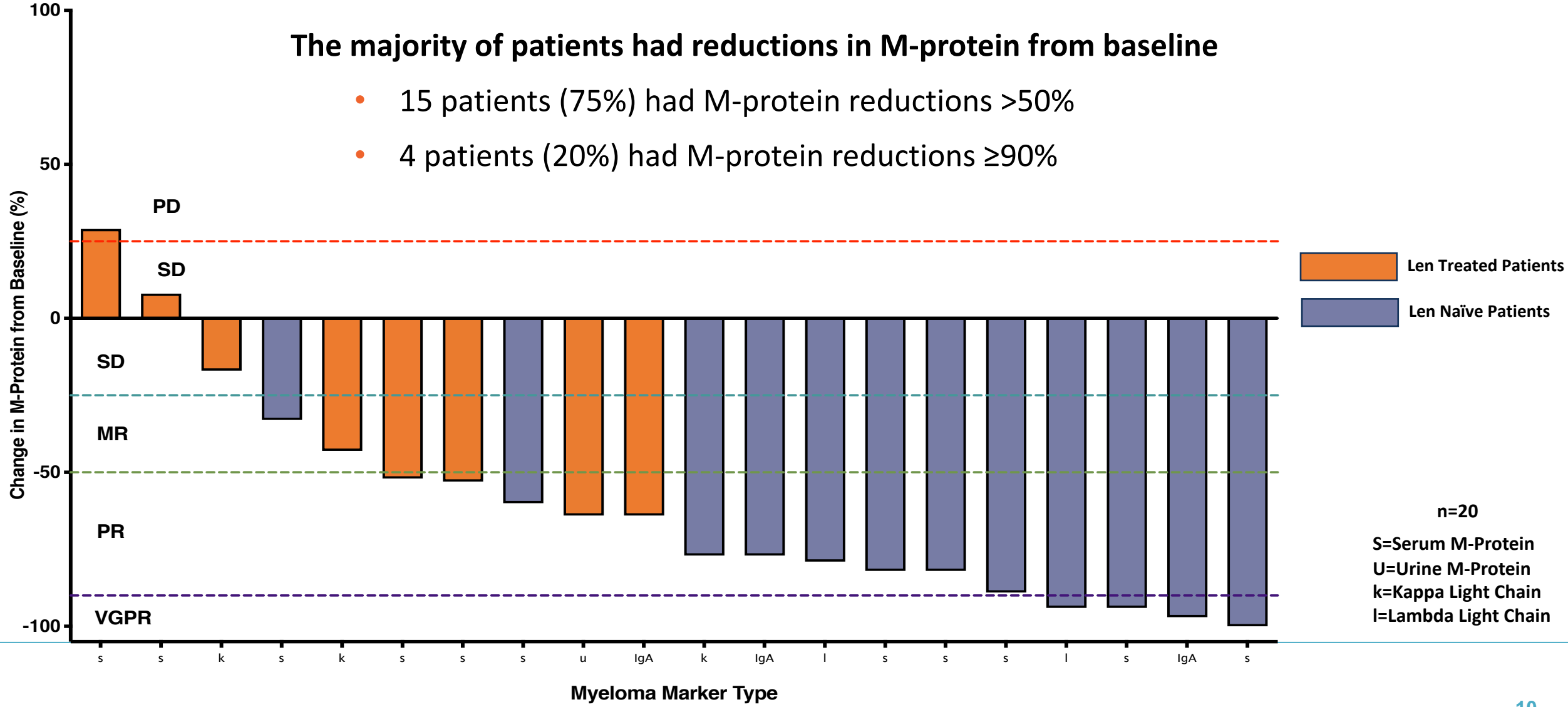
Selinexor Dose	Median Weeks on Treatment (range)	Dose Escalation DLT Evaluable Patients Enrolled (Number of Patients with DLT)	Dose-Limiting Toxicity (DLT)
60 mg BIW	6 (2-25)	**5 (4)**	G3 anorexia and weight loss, G4 thrombocytopenia, G4 thrombocytopenia and G3 fatigue, 4 missed doses
80 mg QW	13 (3-155)	**6 (2)**	G4 thrombocytopenia (2 cases)
60 mg QW	23 (2-122)	**6 (-)**	No DLTs were reported in the 60 mg QW cohort

Based on tolerability, the RP2D of SRd is selinexor 60 mg QW, lenalidomide 25 mg QD, and dexamethasone 40 mg QW

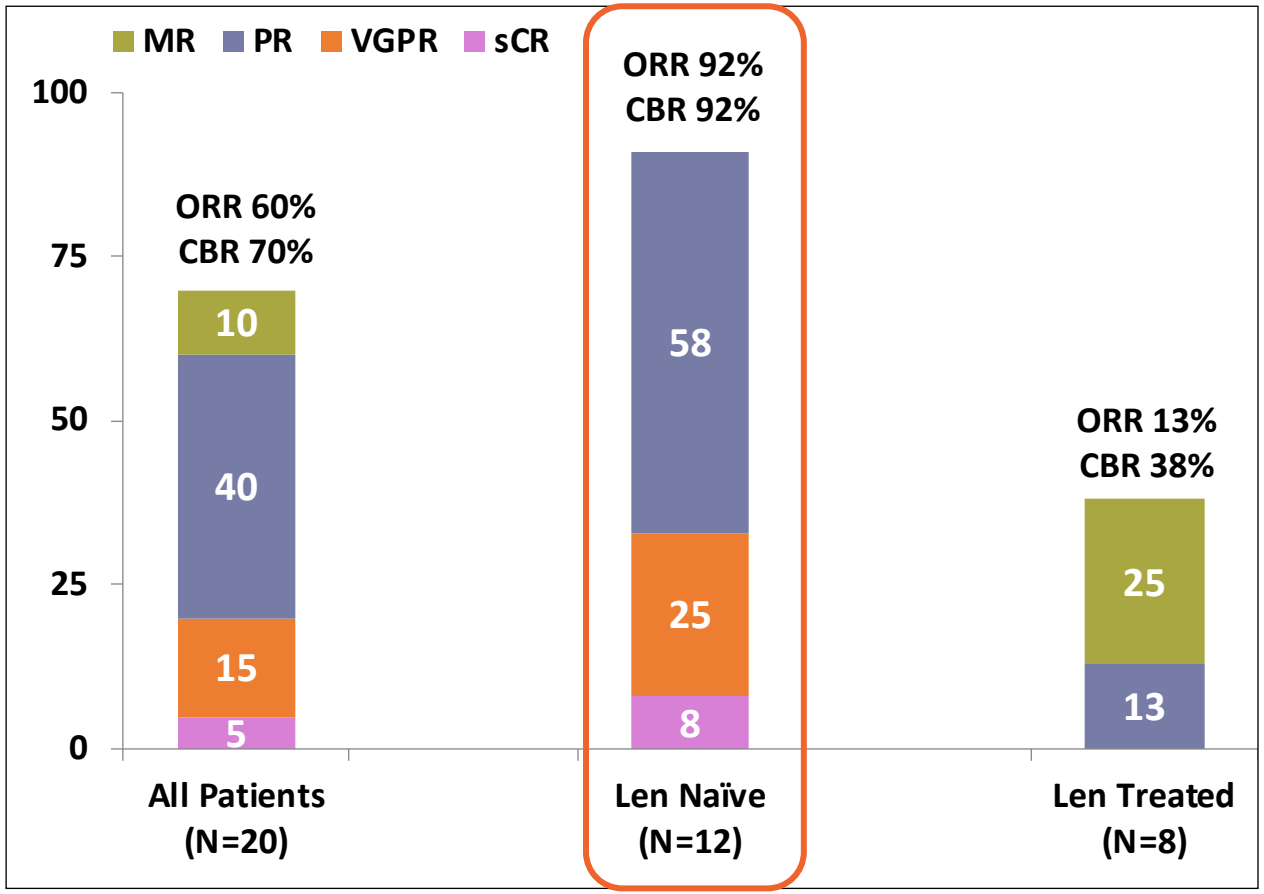
SRd Efficacy – M-Protein Effect

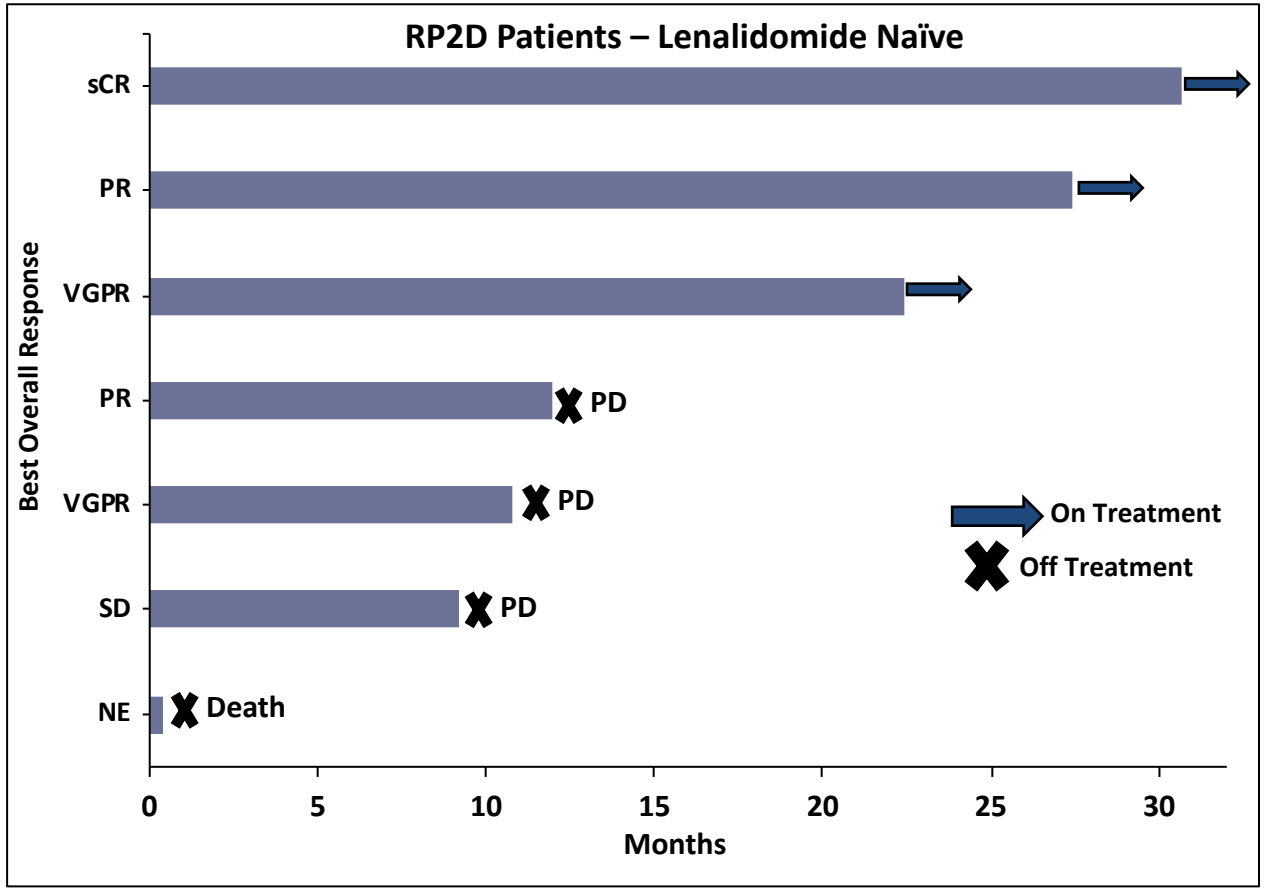
The majority of patients had reductions in M-protein from baseline

- 15 patients (75%) had M-protein reductions >50%
- 4 patients (20%) had M-protein reductions ≥90%



Selinexor-Lenalidomide-Dexamethasone: Efficacy





- The median time to response (≥PR) was 1 month
- Among lenalidomide naïve RP2D patients, the median time on treatment was 12 months

Responses were adjudicated according to the *International Myeloma Working Group* criteria,*four patients not evaluable for response withdrew consent prior to disease follow-up. Two unconfirmed PRs, ORR=Overall Response Rate (sCR+VGPR+PR), CBR=Clinical Benefit Rate (ORR+MR), sCR=Stringent Complete Response, VGPR=Very Good Partial Response, PR=Partial Response, MR=Minimal Response. Responses as of August 1, 2019 based on interim unaudited data.

Conclusions – Safety & Efficacy

- **Selinexor is first in class XPO1 inhibitor now approved for RRMM**
- **Weekly Selinexor** 60 mg QW can be safely combined with full dose lenalidomide 25 mg QD, and dexamethasone 40 mg QW
- **Side Effect profile is consistent with no new signal**
  - **Most Common G3/4 AEs –** thrombocytopenia and neutropenia
  - **Low-grade Gastrointestinal Side Effects –** common and expected, and can be managed with appropriate supportive care and/or dose modifications
- **Combination is highly active with ORR – 92%** in lenalidomide-naïve patients
- **Combination is being evaluated in NDMM**

All oral combination of selinexor / lenalidomide / dexamethasone appears to be highly active, well tolerated and warrants further investigation

Acknowledgments

Patients, their families, and caregivers
Investigators, co-investigators, and study teams at each participating center

- Dalhousie University and QEII Health Sciences Center, Halifax, Nova Scotia
- Duke University Cancer Center, Durham, North Carolina
- Columbia University, New York, NY
- UCLA Ronald Reagan Medical Center, Los Angeles, California
- Swedish Cancer Center, Seattle, WA
- Southern Alberta Cancer Research Institute, Calgary, Alberta
- Vancouver General Hospital, Vancouver, British Columbia
- Royal Victoria Hospital, Montreal, Québec
- Cancer Care Manitoba, Winnipeg, Manitoba
- Cross Cancer Institute, Edmonton, Alberta
- Hôpital Maisonneuve-Rosemont, Montreal, Québec
- Princess Margaret Cancer Center, Toronto, Ontario
- Myeloma Canada, Laval, Québec
- University of Rochester Medical College, New York, NY
- Moffitt Cancer Center, Tampa, FL
- University of Nebraska Medical Center
- University of Wisconsin Carbone Cancer Center

This study was sponsored by Karyopharm Therapeutics