Safety and Efficacy of the Combination of Selinexor, Daratumumab, and Dexamethasone (SDd) in Patients with Multiple Myeloma (MM) Previously Exposed to Proteasome Inhibitors and Immunomodulatory Drugs

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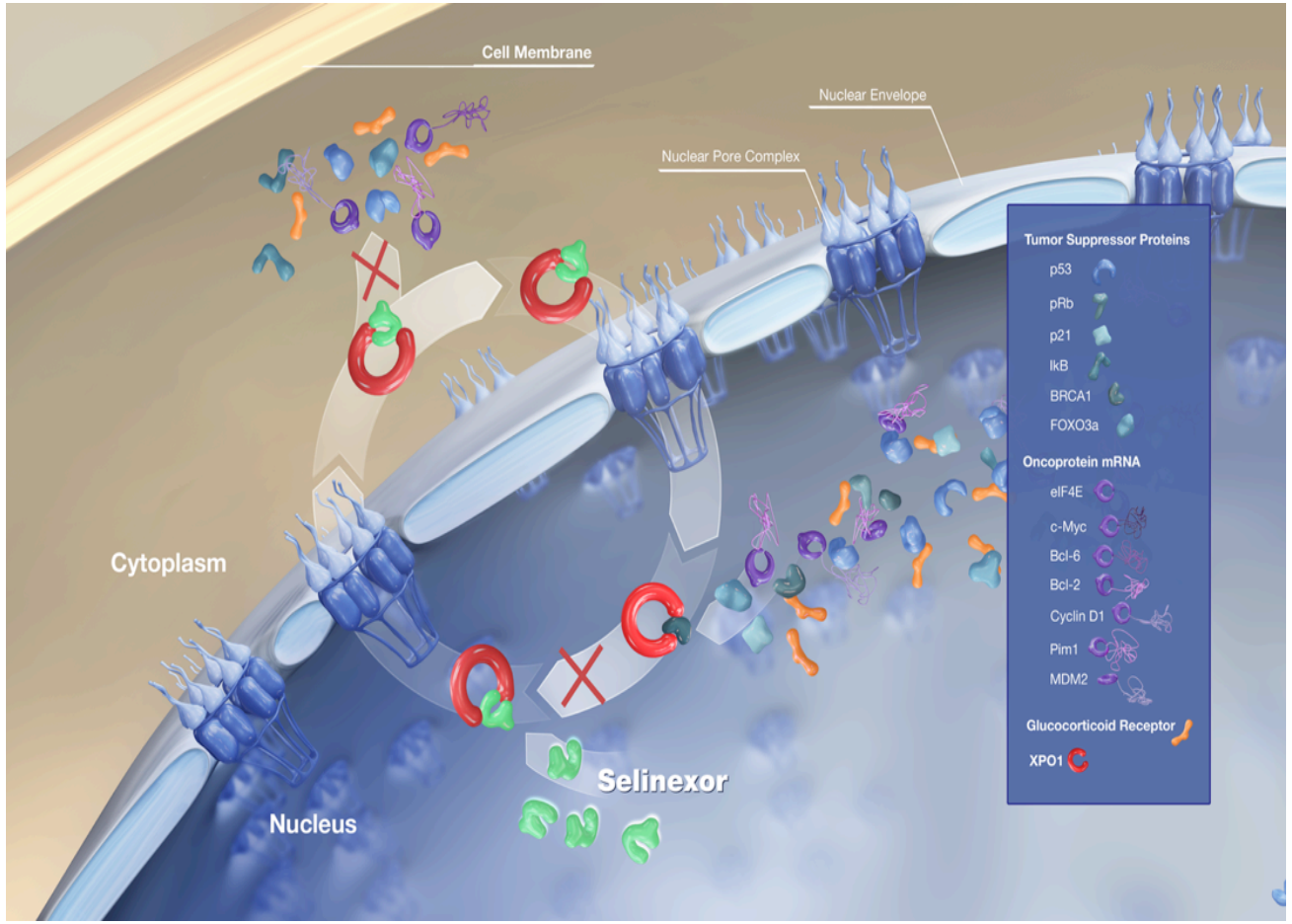
Selinexor:

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

Enhances daratumumab activity *in-vitro* against myeloma cells

[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et al., Leukemia, 2013, [2]Tai et al., Leukemia, 2013, [3]Argueta et al., Oncotarget, 2018 [4]Turner et al, 2017 unpublished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: Daratumumab and Selinexor Activity in Heavily-Treated MM

SIRIUS: Daratumumab[1]

Refractory to **PI** and **IMiD**

ORR: 29.2% (Overall)
ORR: 21.2% (Quad-Ref)
PFS: 3.7 months (Overall)

STORM: Selinexor + Dexamethasone[2]

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

ORR: 26.2%
ORR: 25.3% (Penta-Ref)
PFS: 3.7 months (Overall)

Both show single agent activity with ORR of 26-29% in RRMM

1. Lonial S, et al. Lancet. 2016;387:1551-60.
2. Chari A, et al. ASH 2018

STOMP Study Design

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

Patient Populations:

- **Arm SDd: selinexor + daratumumab + dexamethasone**
  - **Patients who received ≥3 prior lines of therapy for MM, including a PI and an IMiD**
  - **Or patients with MM refractory to both a PI and an IMiD**
- Arm SPd: selinexor + pomalidomide + dexamethasone *(EHA 2019 – Poster PF587)*
- Arm SVd: selinexor + bortezomib + dexamethasone
- Arm SKd: selinexor + carfilzomib + dexamethasone *(EHA 2019 – Poster PS1414)*
- Arm SRd: selinexor + lenalidomide + dexamethasone: >1 therapy and in patients with newly diagnosed MM

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

Dose Level	Treatment Regimen	Patients Enrolled (Number of Patients with DLT)	Dose-Limiting Toxicity (DLT)
0	Selinexor, oral 60 mg (Days 1, 3) Twice Weekly Daratumumab, IV 16 mg/kg Once Weekly Dexamethasone, oral 20 mg Twice Weekly	**3 (2)**	Grade 2 fatigue and Grade 3 thrombocytopenia (both requiring reduction to 100 mg QW selinexor)
-1	Selinexor, oral 100 mg Once Weekly Daratumumab, IV 16 mg/kg Once Weekly Dexamethasone, oral 40 mg Once Weekly	**6 (-)**	No DLTs were reported in the 100 mg QW cohort

Patient Characteristics

Patient Characteristics	N
Enrolled as of May 1, 2019 60 mg selinexor BIW + 16 mg/kg daratumumab QW **100 mg selinexor QW + 16 mg/kg daratumumab QW (RP2D)**	**34** 3 **31**
Median Age, Years (range)	**68** (44 – 83)
Males : Females	**19** (56%) : **15** (44%)
Median Time from Diagnosis to SDd Treatment, Years (range)	5.6 (<1 – 14)
Median Prior Regimens (range) Proteasome Inhibitor (Treated: Refractory) Immunomodulatory Drug (Treated: Refractory) Autologous Stem Cell Transplant Daratumumab Treated	**3 (2–10)** 34 (100%) : 29 (85%) 34 (100%) : 26 (76%) 24 (71%) 2 (6%)

Treatment-Related Non-Hematological Adverse Events in ≥10% Patients (RP2D Patients)

AE Term	100 mg Sel QW + 16 mg/kg Dara QW RP2D			
Gastrointestinal	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=31)**
Nausea	19 (61.3)	2 (6.5)	--	**21 (67.7)**
Dysgeusia	11 (35.5)	--	--	**11 (35.5)**
Diarrhea	9 (29.0)	1 (3.2)	--	**10 (32.3)**
Anorexia	10 (32.3)	--	--	**10 (32.3)**
Vomiting	8 (25.8)	--	--	**8 (25.8)**
Constipation	5 (16.1)	--	--	**5 (16.1)**
Constitutional				
Fatigue	13 (41.9)	5 (16.1)	--	**18 (58.1)**
Dizziness	5 (16.1)	--	--	**5 (16.1)**
Weight Loss	4 (12.9)	--	--	**4 (12.9)**
Other				
Hyponatremia	6 (19.4)	4 (12.9)	--	**10 (32.3)**
Insomnia	10 (32.3)	--	--	**10 (32.3)**
Vision Blurred	9 (29.0)	--	--	**9 (29.0)**
Hyperglycemia	5 (16.1)	1 (3.2)	--	**6 (19.4)**
Infusion Related Reaction	3 (9.7)	1 (3.2)	--	**4 (12.9)**

Safety data cutoff of May 1, 2019

Treatment-Related Hematological Adverse Events in ≥10% Patients (RP2D Patients)

AE Term	100 mg Sel QW + 16 mg/kg Dara QW RP2D			
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=31)**
Thrombocytopenia	8 (25.8)	8 (25.8)	5 (16.1)	**21 (67.7)**
Anemia	9 (29.0)	9 (29.0)	--	**18 (58.1)**
Neutropenia	6 (19.4)	7 (22.6)	--	**13 (41.9)**
Leukopenia	4 (12.9)	8 (25.8)	--	**12 (38.7)**
Lymphopenia	1 (3.2)	3 (9.7)	1 (3.2)	**5 (16.1)**

- No treatment-related Grade 5 events were reported

Based on tolerability, the RP2D of SDd is selinexor 100 mg QW, daratumumab 16 mg/kg (per approved dosing) and dexamethasone 40 mg QW

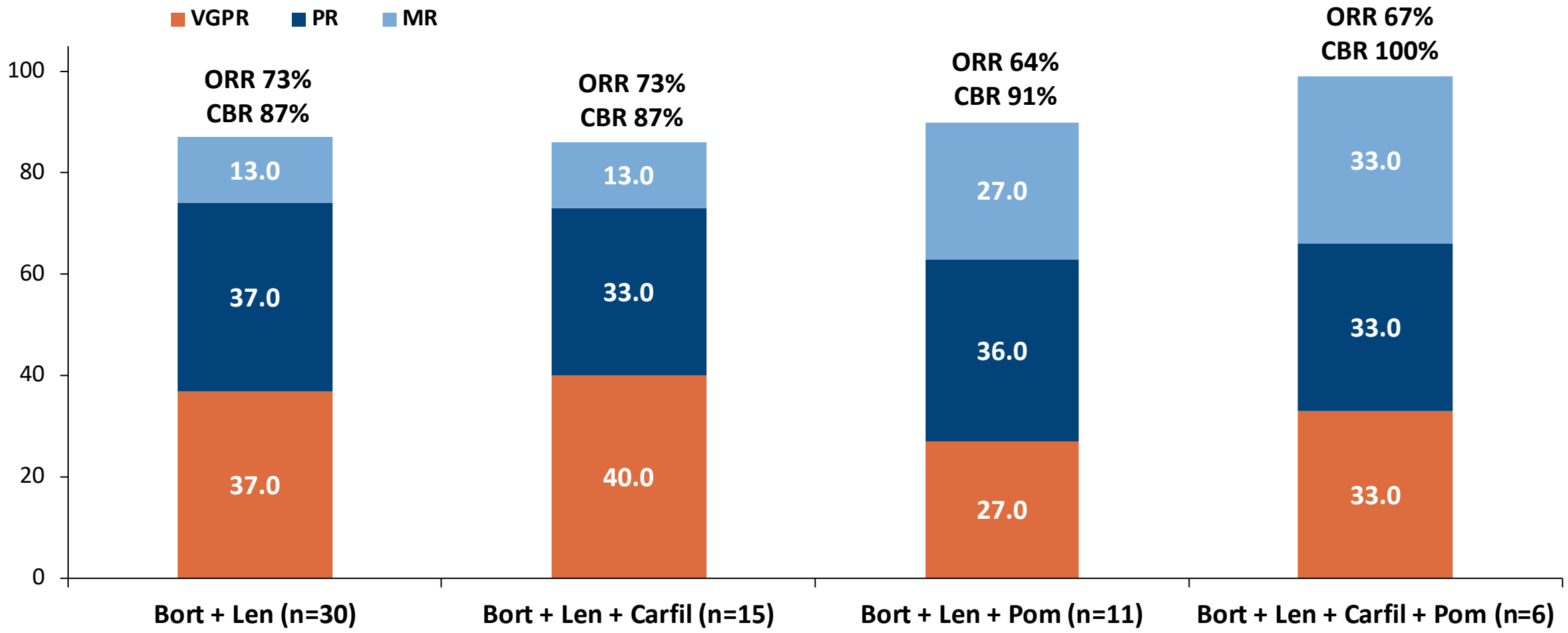
Safety data cutoff of May 1, 2019

Selinexor-Daratumumab-Dex: Efficacy

Category	N*	ORR (%)	VGPR (%)	PR‡ (%)	CBR (%)	MR‡ (%)	SD (%)	PD (%)
Daratumumab Naïve	30	**22 (73%)**	**11 (37%)**	**11 (37%)**	26 (87%)	4 (13%)	4 (13%)	--
All	32	**22 (69%)**	**11 (34%)**	**11 (34%)**	26 (81%)	4 (13%)	5 (16%)	1 (3%)

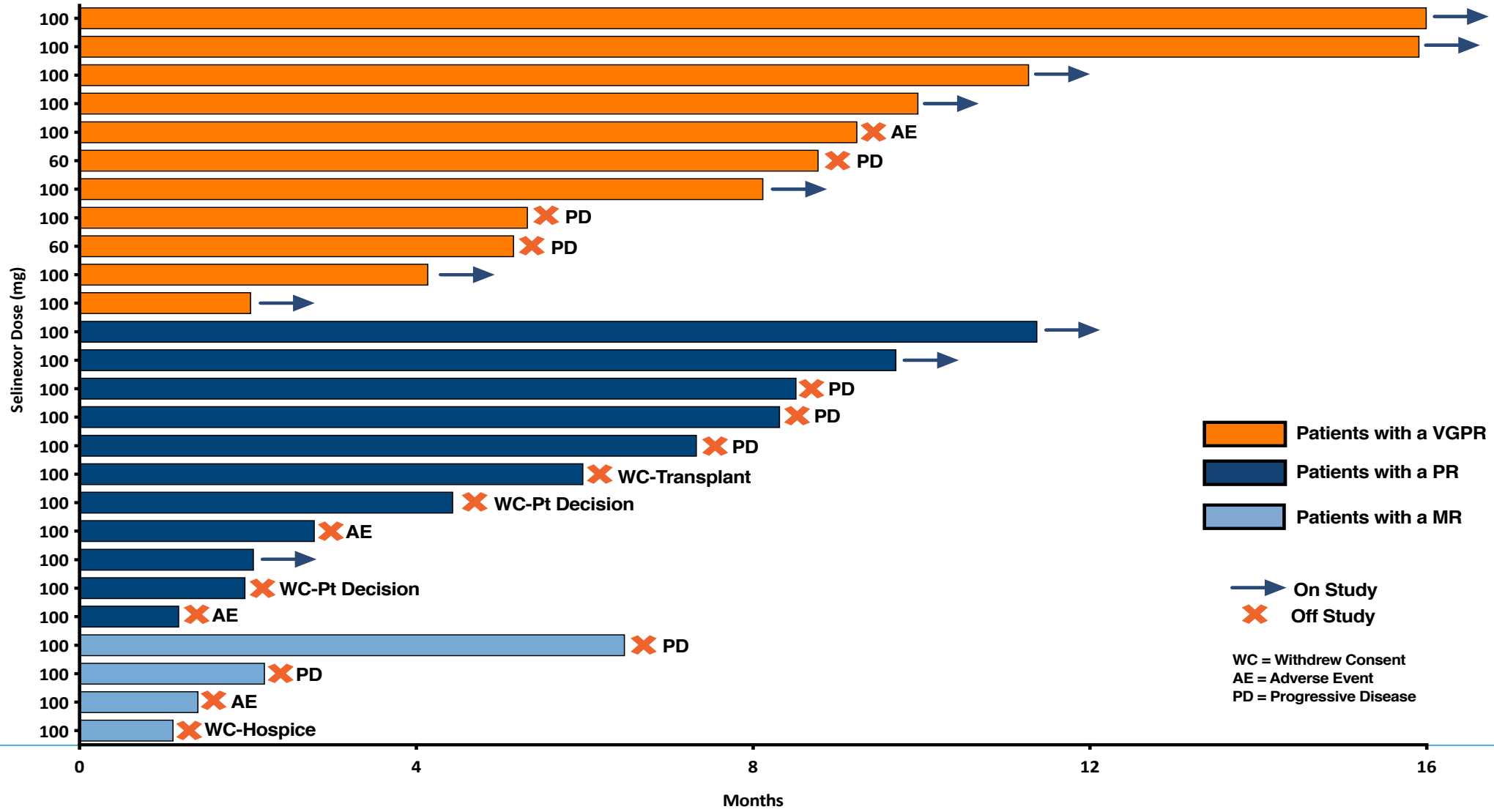
Responses were adjudicated according to the *International Myeloma Working Group* criteria,*two patients not evaluable for response withdrew consent prior to disease follow-up. ‡Two unconfirmed PRs, one unconfirmed MR. ORR=Overall Response Rate (VGPR+PR), VGPR=Very Good Partial Response, PR=Partial Response,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

SDd Efficacy by Prior Exposure : Dara-Naïve Patients (Efficacy Preserved Regardless of Prior Treatment)



MR=Minimal Response; PR=Partial Response; VGPR=Very Good Partial Response; N=Number

SDd Efficacy – Patients with CBR (≥MR)

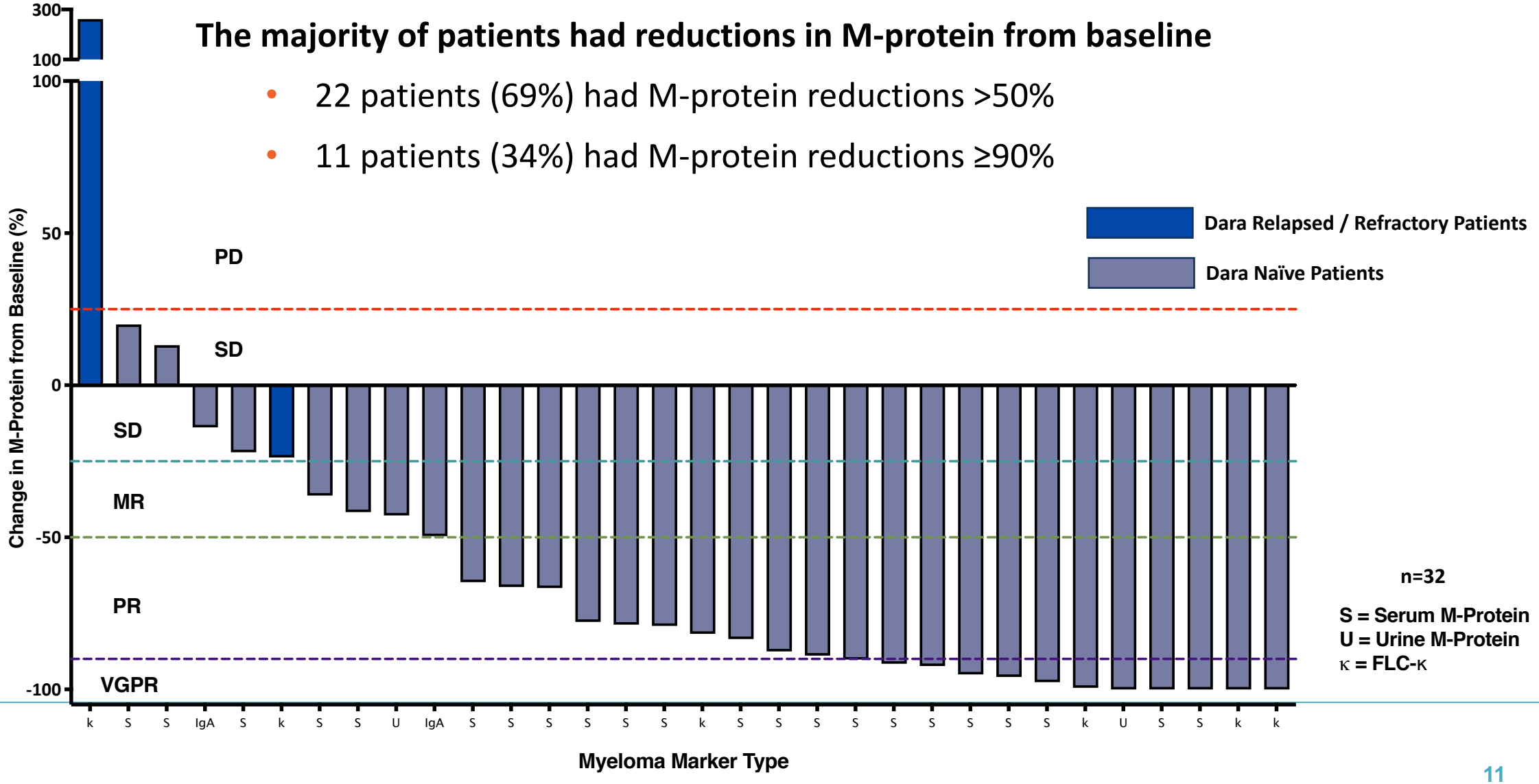


- Among patients with a response **≥PR** the median time on treatment was **7.7** months
- Median time to response was **1** month

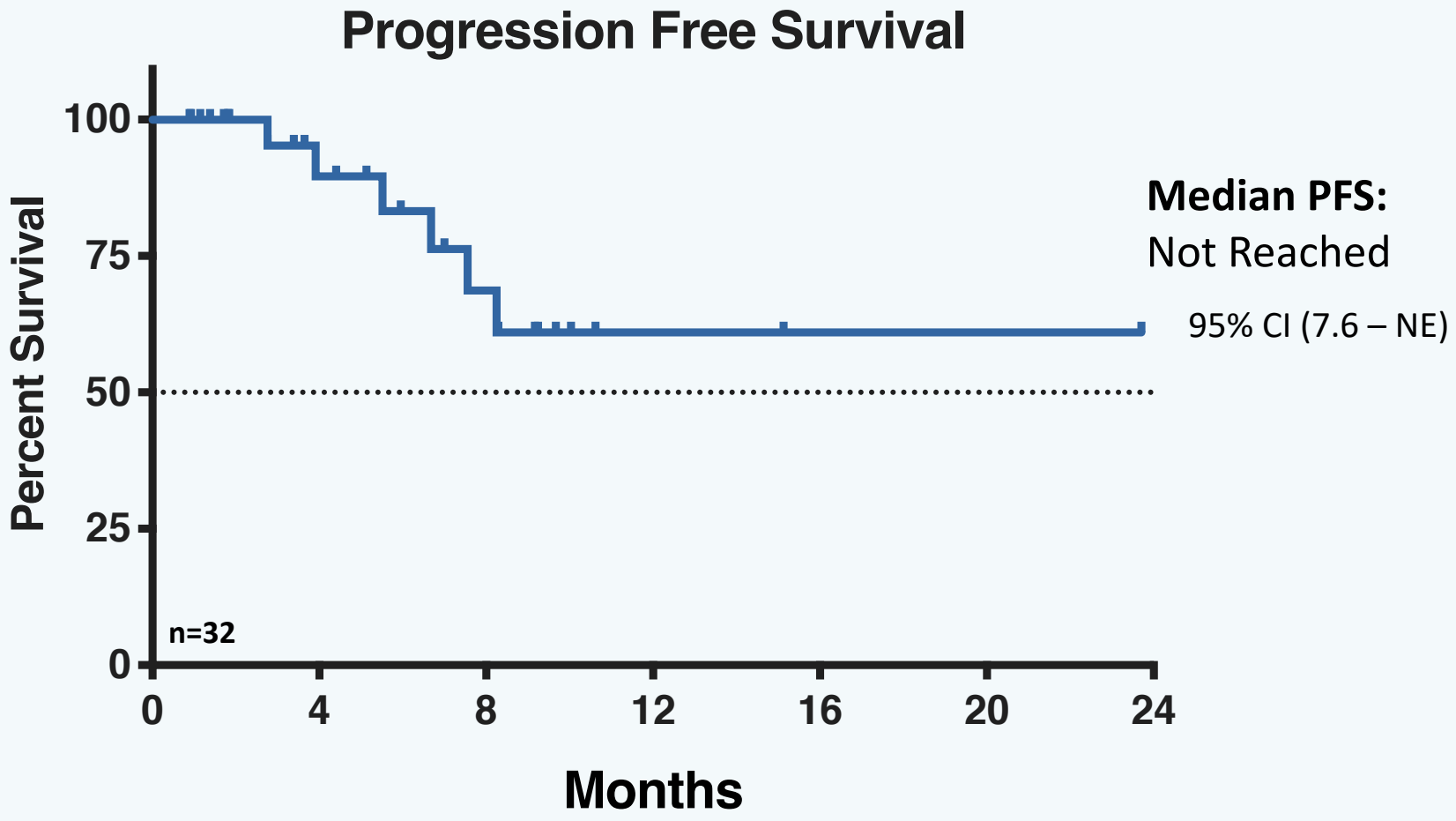
SDd Efficacy – M-Protein Effect

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

- 22 patients (69%) had M-protein reductions >50%
- 11 patients (34%) had M-protein reductions ≥90%



Progression Free Survival



Conclusions – Safety & Efficacy

- **RP2D of SDd –** selinexor 100 mg, daratumumab 16 mg/kg and dexamethasone 40 mg, administered QW
- **Most Common G3/4 AEs –** thrombocytopenia, anemia, leukopenia, and neutropenia
- **Low-grade Gastrointestinal Side Effects –** common and expected, and can be managed with appropriate supportive care and/or dose modifications
- **ORR –** 73% in daratumumab-naïve patients
  - ~29% with daratumumab or 26% with selinexor alone
- **Clinical Benefit Rate –** 87% in daratumumab-naïve patients
- **Medians –** PFS and DOR medians have not been reached

Selinexor in combination with daratumumab/dexamethasone appears to be highly active, produces deep and durable responses in patients with RRMM, and warrants further investigation

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