Deep and Durable Responses with Selinexor, Daratumumab, and Dexamethasome (SDd) in Patients with Multiple Myeloma Previously Treated with PIs and IMiDs: Results of Phase 1b/2 Study of SDd

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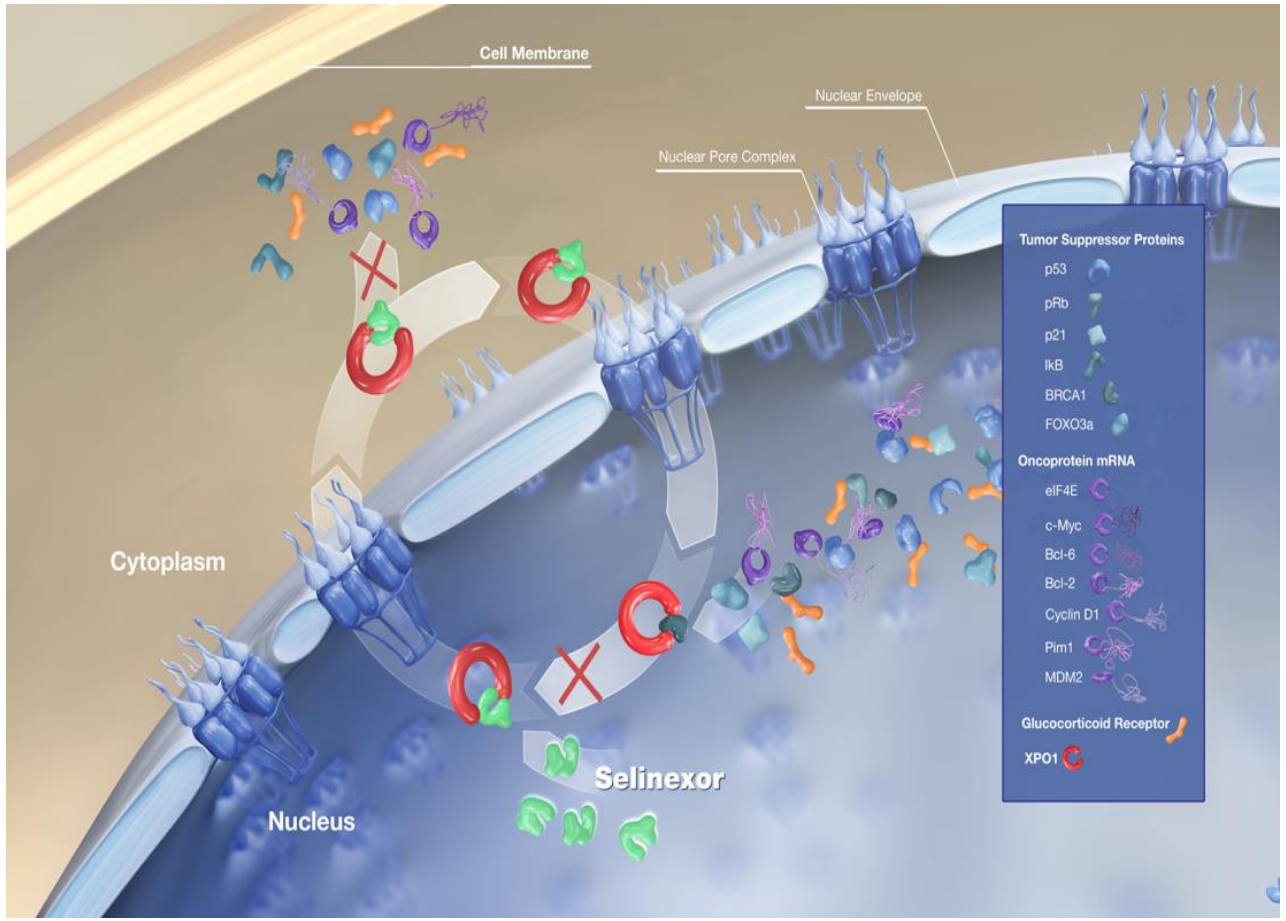
Selinexor:

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et al., Leukemia, 2013, [2]Tai et al., Leukemia, 2013, [3]Argueta et al., Oncotarget, 2018 [4]Turner et al, 2017 unpublished

Daratumumab and Selinexor Single Agent Activity in Heavily-Treated MM

SIRIUS: Daratumumab Monotherapy[1]

Refractory to PI and IMiD

ORR: 29.2%

STORM: Selinexor + Dexamethasone[2]

Refractory to PI, IMiD and Dara

ORR: 26.2%

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 Abstract

STOMP Study Design

Primary Objective: 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 *(ASH 2018 - Poster 1993)*
- Arm SVd: selinexor + bortezomib + dexamethasone
- Arm SKd: selinexor + carfilzomib + dexamethasone
- Arm SRd: selinexor + lenalidomide + dexamethasone (also in newly-diagnosed patients)

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

Dose Level	Treatment Regimen	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	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	No DLTs were reported in the 100 mg QW cohort

SDd Patient Characteristics

Patient Characteristics	N
Enrolled as of November 15, 2018 60 mg selinexor BIW + 16 mg/kg daratumumab QW **100 mg selinexor QW + 16 mg/kg daratumumab QW (RP2D)**	**28** 3 **25**
Median Age, Years (range)	68 (44–77)
Males : Females	14 M : 14 F
Median Time from Diagnosis to SDd Treatment, Years (range)	5.9 (<1–12.9)
Median Prior Regimens (range) Proteasome Inhibitor (Exposed : Refractory) Immunomodulatory Drug (Exposed : Refractory) Autologous Stem Cell Transplant Daratumumab	**3 (2–10)** 28 (100%) : 17 (61%) 28 (100%) : 18 (64%) 22 (79%) 2 (7%)

SDd: Treatment Related Non-Hematological Adverse Events in >3 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=25)**
Nausea	14 (56.0%)	1 (4.0%)	--	**15 (60.0%)**
Diarrhea	7 (28.0%)	1 (4.0%)	--	**8 (32.0%)**
Vomiting	6 (24.0%)	--	--	**6 (24.0%)**
Anorexia	7 (28.0%)	--	--	**7 (28.0%)**
Constipation	4 (16.0%)	--	--	**4 (16.0%)**
Dysgeusia	5 (20.0%)	--	--	**5 (20.0%)**
Constitutional				
Fatigue	9 (36.0%)	3 (12.0%)	--	**12 (48.0%)**
Dyspnea	2 (8.0%)	--	--	**2 (8.0%)**
Weight Loss	2 (8.0%)	--	--	**2 (8.0%)**
Other				
Hyponatremia	4 (16.0%)	3 (12.0%)	--	**7 (28.0%)**
Insomnia	6 (24.0%)	--	--	**6 (24.0%)**
Vision Blurred	6 (24.0%)	--	--	**6 (24.0%)**

Safety data cutoff of November 1, 2018

SDd: Treatment Related Hematological Adverse Events in >3 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=25)**
Thrombocytopenia	5 (20.0%)	7 (28.0%)	4 (16.0%)	**16 (64.0%)**
Anemia	5 (20.0%)	7 (28.0%)	--	**12 (48.0%)**
Leukopenia	4 (16.0%)	7 (28.0%)	--	**11 (44.0%)**
Neutropenia	5 (20.0%)	6 (24.0%)	--	**11 (44.0%)**
Lymphopenia	1 (4.0%)	3 (12.0%)	1 (4.0%)	**5 (20.0%)**

- 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 November 1, 2018

MTD, Maximum Tolerated Dose; DLT, Dose Limiting Toxicity

SDd Efficacy

Category	N*	ORR (%)	VGPR (%)	PR‡ (%)	MR (%)	CBR (%)	SD (%)	PD (%)
Daratumumab Naïve	24	**19 (79%)**	**7 (29%)**	**12 (50%)**	2 (8%)	21 (88%)	3 (13%)	--
All	26	**19 (73%)**	**7 (27%)**	**12 (46%)**	2 (8%)	21 (81%)	4 (15%)	1 (4%)

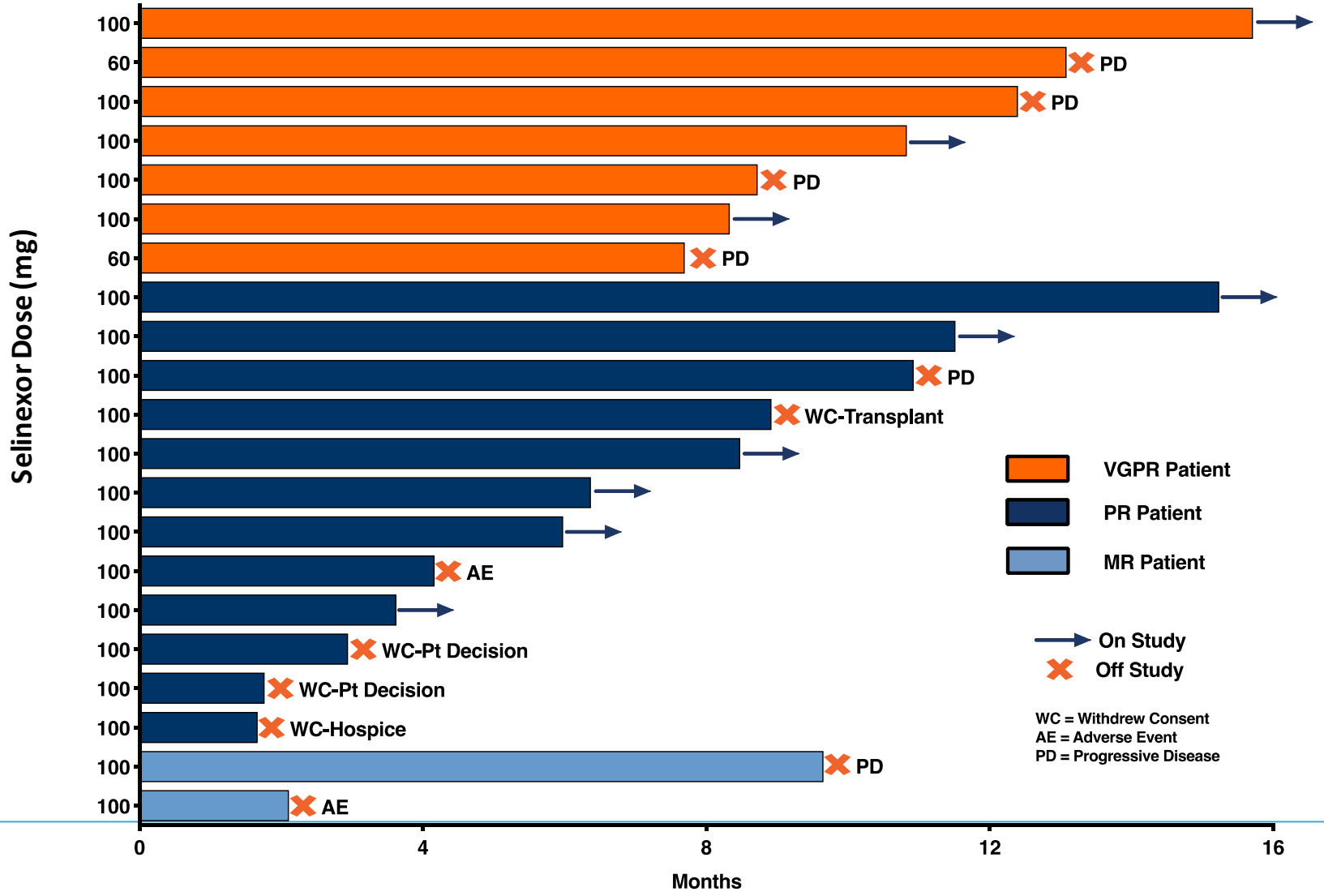
Responses were adjudicated according to the *International Myeloma Working Group* criteria,*two patients not evaluable for response withdrew consent prior to disease follow-up. ‡Two unconfirmed PRs. ORR=Overall Response Rate (VGPR+PR), VGPR=Very Good Partial Response, PR=Partial Response, MR=Minimal Response, SD=Stable Disease, PD=Progressive Disease, CBR=Clinical Benefit Rate (ORR+MR). Responses as of November 15, 2018 based on interim unaudited data.

SDd Efficacy: Dara-Naïve Patients

Prior Therapy Exposure	N*	ORR (%)	VGPR (%)	PR‡ (%)	MR (%)	CBR (%)	SD (%)	PD (%)
Bort + Len	24	**19 (79%)**	**7 (29%)**	**12 (50%)**	2 (8%)	21 (88%)	3 (13%)	--
Bort + Len + Carfil	13	**11 (85%)**	**4 (31%)**	**7 (54%)**	1 (8%)	12 (92%)	1 (8%)	--
Bort + Len + Pom	10	**7 (70%)**	**2 (20%)**	**5 (50%)**	2 (20%)	9 (90%)	1 (10%)	--
Bort + Len + Carfil + Pom	6	**5 (83%)**	**1 (17%)**	**4 (67%)**	1 (17%)	6 (100%)	--	--

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.
ORR=Overall Response Rate (VGPR+PR), VGPR=Very Good Partial Response, PR=Partial Response, MR=Minor Response, SD=Stable Disease, PD=Progressive Disease, CBR=Clinical Benefit Rate (ORR+MR).
Responses as of November 15th, 2018 based on interim unaudited data.

SDd Efficacy – Patients with CBR (≥MR)

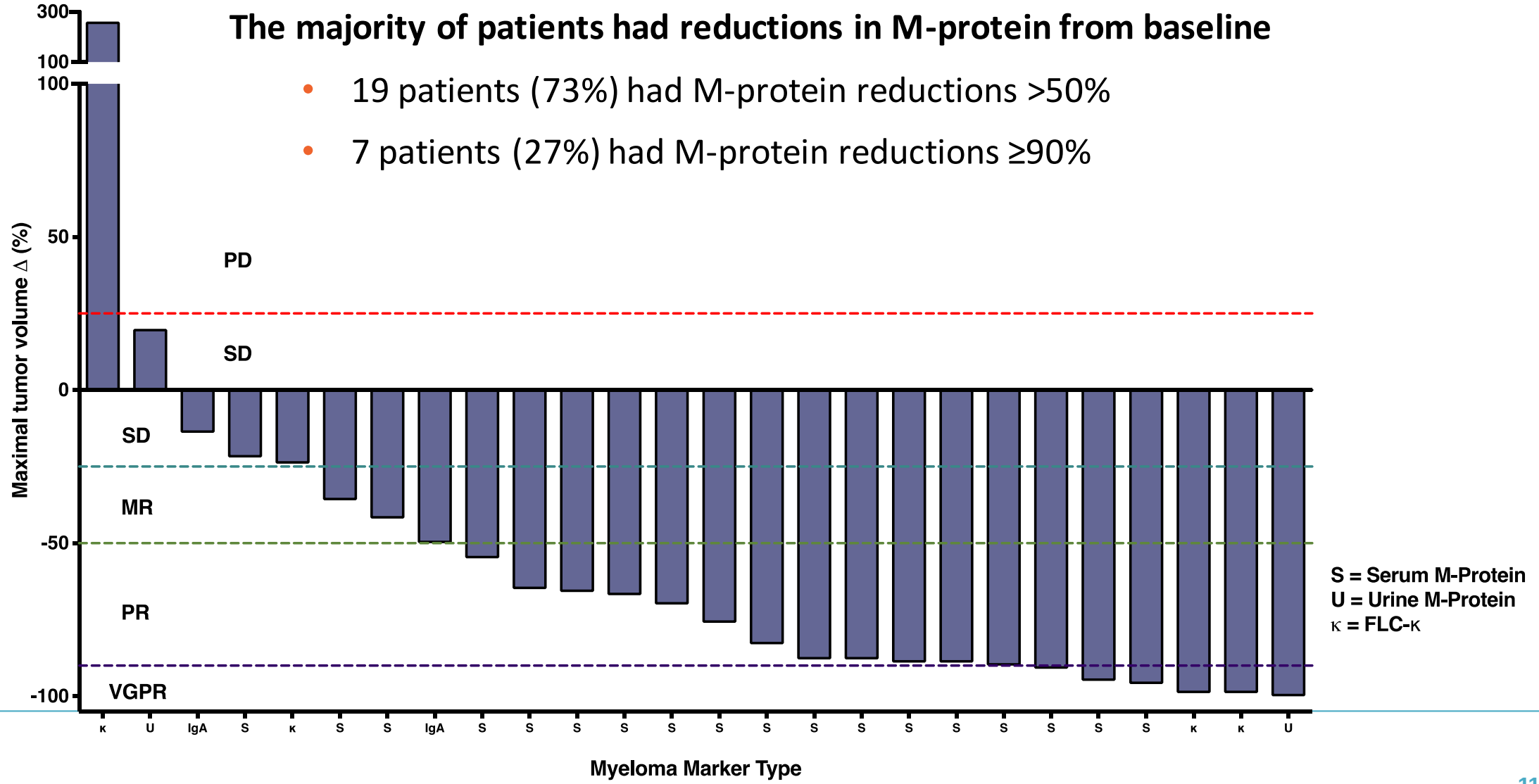


- Among patients ≥PR the median time on treatment was **7.3** months
- Median time on study for all patients was **5.8** months with a median follow up of **7.7** months
- Median time to response was **1** month

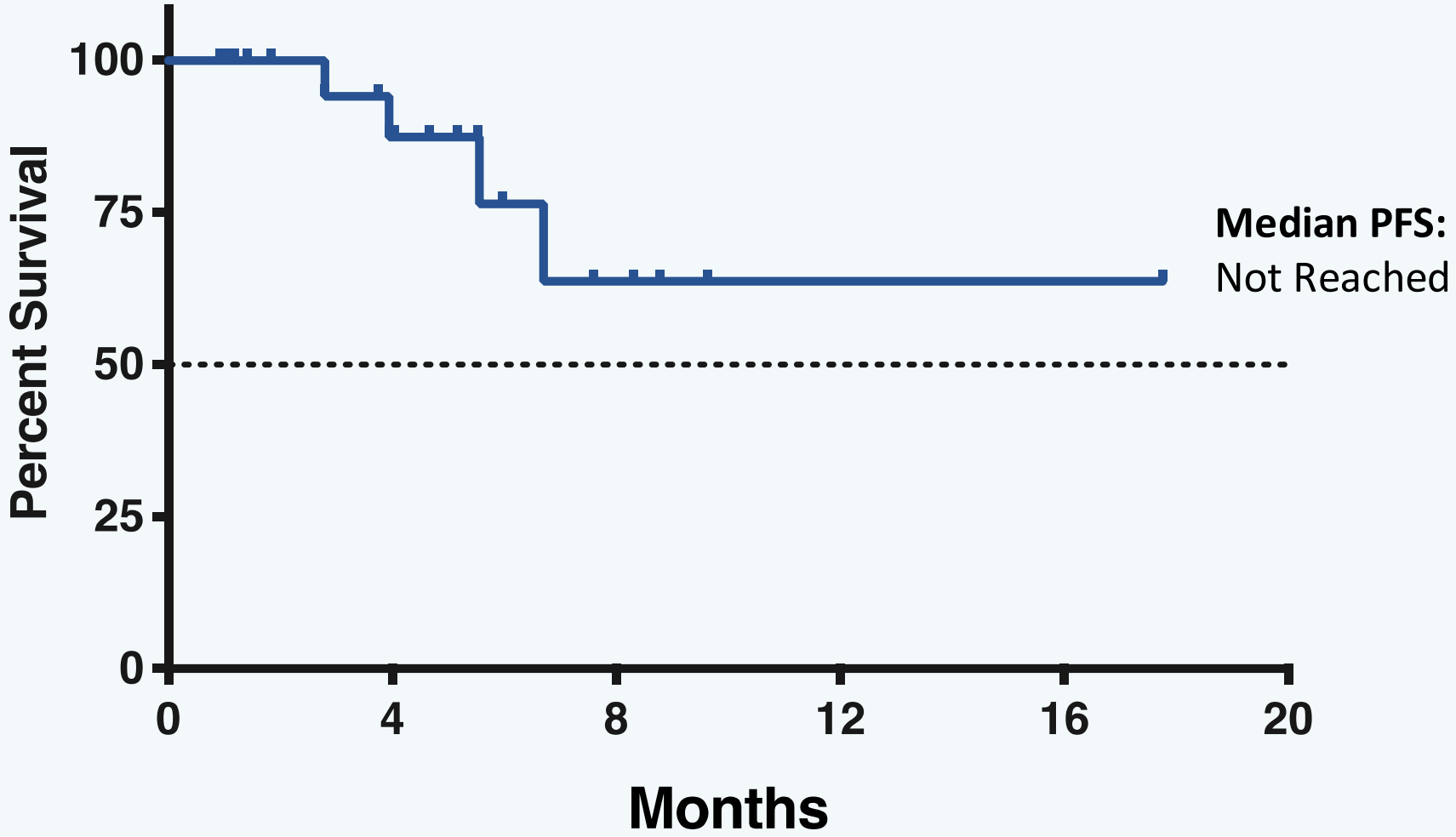
SDd Efficacy – M-Protein Effect

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

- 19 patients (73%) had M-protein reductions >50%
- 7 patients (27%) had M-protein reductions ≥90%



SDd: Progression Free Survival



Conclusions – Safety & Efficacy

Selinexor in combination with daratumumab and dexamethasone:

- RP2D of SDd: selinexor 100 mg, daratumumab 16 mg/kg and dexamethasone 40 mg, administered QW
- Most common G3/4 AEs: thrombocytopenia (44%), anemia (28%), leukopenia (28%), and neutropenia (24%)
- Low-grade gastrointestinal side effects were common

Selinexor in combination with daratumumab and dexamethasone achieved:

- **ORR of 79%** in daratumumab-naïve patients
- Clinical benefit rate of 88% in daratumumab-naïve patients
- Medians for PFS and DOR have not been reached

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

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