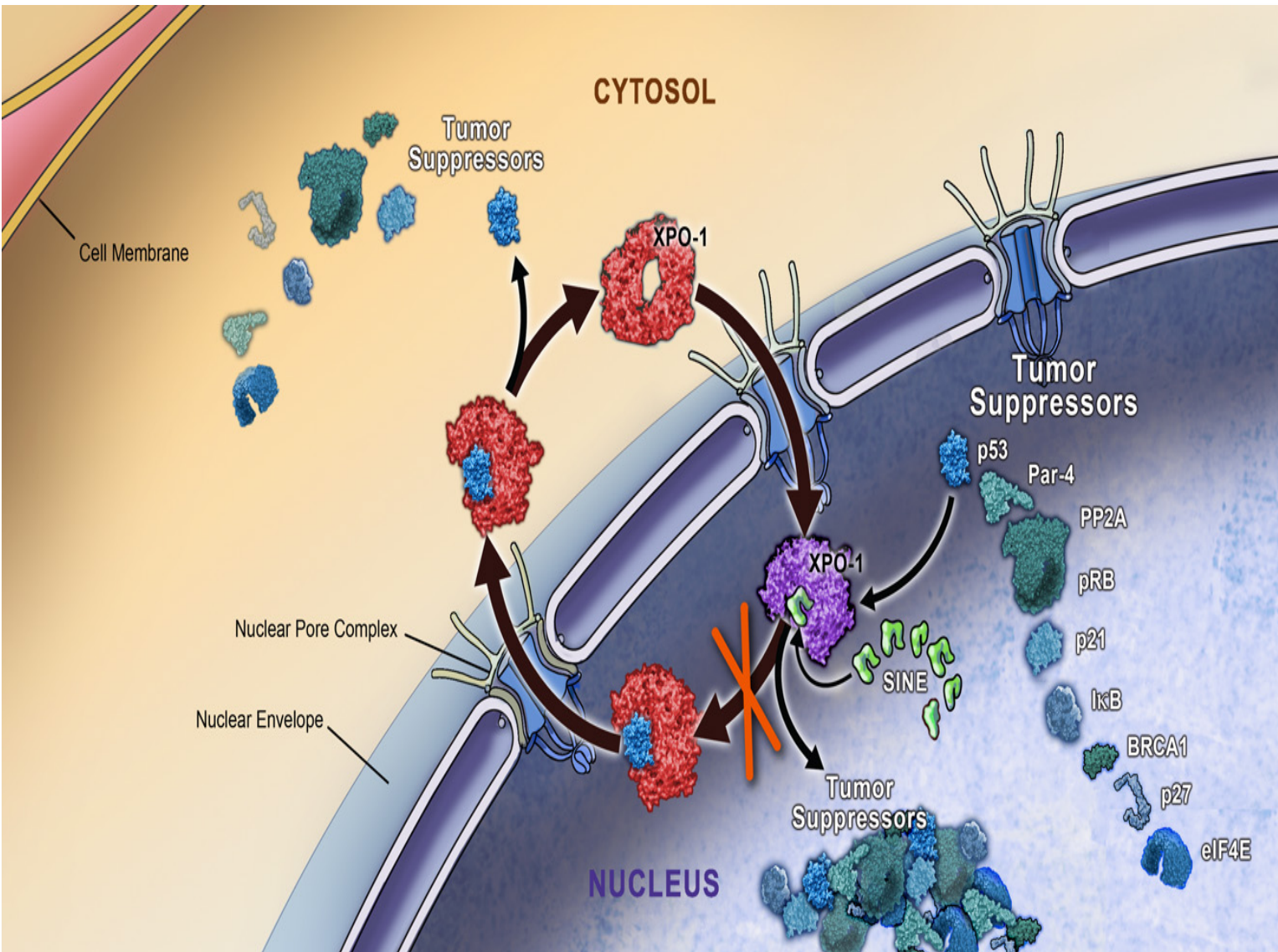


A Phase Ib/II Trial of Selinexor Combined with Lenalidomide and Low Dose Dexamethasone (SRd) in Patients with Relapsed / Refractory Multiple Myeloma

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Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, BCL-xL, MDM2, cyclins)
- Selinexor, an oral selective inhibitor of XPO1-mediated nuclear export (SINE) compound, reactivates multiple TSPs relevant to MM including p53, IκB and FOXO, reactivates the GR when given with steroids, reduces c-Myc levels, and overcomes MDM2-mediated p53 degradation
- Selinexor has demonstrated single agent activity in patients with heavily pretreated refractory myeloma
- Selinexor demonstrated synergistic activity in combination with pomalidomide and lenalidomide *in vitro* and *in vivo*

STOMP Study Design

- **Selinexor and backbone Treatments Of multiple Myeloma Patients (STOMP)** is an open label, randomized (once vs. twice weekly dosing), dose escalation (Phase I) and expansion (Phase II) combination study in patients with relapsed/refractory multiple myeloma
- **Objectives:**
 - Primary: maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
 - Secondary: overall response rate (ORR) and duration of response (DOR) for each arm independently
- **Dose Limiting Toxicity (DLT) Definition: Evaluable in Dose Escalation Cycle 1 Only**
 - >1 missed dose (out of 4 doses – once-weekly selinexor dose schedules), or >2 missed doses (out of 6 doses – twice weekly dose schedules) of selinexor during a cycle due to study-drug related toxicity
 - Discontinuation of a patient before completing Cycle 1, due to study-drug related toxicity
 - Grade 3 nausea, vomiting, dehydration, diarrhea or fatigue lasting >3 days despite optimal supportive medications
 - Grade 4 neutropenia lasting > 7 days or Grade \geq 3 thrombocytopenia with clinically significant bleeding, petechiae or purpura

STOMP Study Design (Cont.)

- **Patient Population SRd:** Patients who received ≥ 1 prior therapy (may include prior lenalidomide (LEN), as long as the patient's MM was not refractory to prior LEN; patients whose MM was refractory to LEN maintenance regimens will be allowed in this cohort)
- **SRd Dose Escalation Scheme:** A standard 3 + 3 design will be used for all dose escalations which contains 2 Cohorts to evaluate QW vs. BIW selinexor dosing. LEN dosing will be 25 mg QD.

Drug	SVd ARM	SPd ARM	SRd ARM	SDd ARM
Selinexor, Oral	60 – 80 mg BIW 80 – 100 mg QW	60 – 80 mg BIW 80 – 100 mg QW	60 – 80 mg BIW 80 – 100 mg QW	60 mg BIW 100 mg QW
Bortezomib, SC	1.3 mg/m ² –QW/BIW	--	--	--
Pomalidomide, PO	--	3 – 4 mg, QD	--	--
Lenalidomide, PO	--	--	25 mg, QD	--
Daratumumab, IV	--	--	--	16 mg/kg, QW
Dexamethasone, Oral	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW

Data presented will focus on the SRd arm. BIW=Twice Weekly, QW=Once Weekly, Dexamethasone will be dosed on selinexor dosing days

SRd Patient Characteristics

SRd Patient Characteristics	N
Patients Enrolled as of November 1, 2017	19
-60 mg selinexor BIW + 25 mg lenalidomide QD	5
-80 mg selinexor QW + lenalidomide QD	6
-60 mg selinexor QW + 25 mg lenalidomide QD (RP2D)	8
Median Age, Years (range)	68 (49 – 84)
Males : Females	13 M : 6 F
Median Years from Diagnosis to SRd Treatment, Years (range)	4 (<1 – 22)
Median Prior Regimens (range)	1 (1 – 7)
-Refractory / Relapsed to Prior Lenalidomide Therapy	5 (26%)
-Lenalidomide Naïve	14 (74%)
-Prior Stem Cell Transplant	8 (42%)
ISS at Diagnosis	
ISS I	1 (5%)
ISS II	7 (37%)
ISS III	4 (21%)
Unknown	7 (37%)

SRd Related Adverse Events ≥ 3 Patients

AE Term	60 mg BIW, 80 mg QW Sel + 25 mg Len QD (N=11)				60 mg Sel QW + 25 mg Len QD RP2D Patients (N=8)				Total (N=19)
	Grade 1/2	Grade 3	Grade 4	Total	Grade 1/2	Grade 3	Grade 4	Total	
Gastrointestinal									
Nausea	7 (63.6%)	--	--	7 (63.6%)	6 (75.0%)	--	--	6 (75.0%)	13 (68.4%)
Anorexia	5 (45.5%)	1 (9.1%)	--	6 (54.5%)	3 (37.5%)	--	--	3 (37.5%)	9 (47.4%)
Constipation	4 (36.4%)	--	--	4 (36.4%)	2 (25.0%)	--	--	2 (25.0%)	6 (31.6%)
Vomiting	3 (27.3%)	--	--	3 (27.3%)	3 (37.5%)	--	--	3 (37.5%)	6 (31.6%)
Diarrhea	2 (18.2%)	--	--	2 (18.2%)	2 (25.0%)	--	--	2 (25.0%)	4 (21.1%)
Altered Taste	3 (27.3%)	--	--	3 (27.3%)	--	--	--	--	3 (15.8%)
Constitutional									
Fatigue	5 (45.5%)	2 (18.2%)	--	7 (63.6%)	3 (37.5%)	1 (12.5%)	--	4 (50.0%)	11 (57.9%)
Weight Loss	4 (36.4%)	--	--	4 (36.4%)	4 (50.0%)	--	--	4 (50.0%)	8 (42.1%)
Hematologic									
Thrombocytopenia	1 (9.1%)	2 (18.2%)	6 (54.5%)	9 (81.8%)	--	3 (37.5%)	2 (25.0%)	5 (62.5%)	14 (73.7%)
Neutropenia	--	4 (36.4%)	2 (18.2%)	6 (54.5%)	--	2 (25.0%)	3 (37.5%)	5 (62.5%)	11 (57.9%)
Anemia	3 (27.3%)	1 (9.1%)	--	4 (36.4%)	--	--	--	--	4 (21.1%)
Other									
Dizziness	2 (18.2%)	--	--	2 (18.2%)	2 (25.0%)	--	--	2 (25.0%)	4 (21.1%)
Muscle Spasms	1 (9.1%)	--	--	1 (9.1%)	3 (37.5%)	--	--	3 (37.5%)	4 (21.1%)

Related Adverse Events SRd Patients: The most common adverse events include: nausea, anorexia, fatigue, (mainly G1/2) neutropenia and thrombocytopenia (mainly G3/4). GI adverse events were generally manageable with antiemetics. Thrombocytopenia was the most common side effect with 4 associated DLTs (2 pts each in the 60 mg BIW and 80 QW cohorts). One additional DLT of grade 3 anorexia was observed in the 60 mg BIW cohort. Thrombocytopenia and anorexia were reduced in the 60 mg QW cohort. Based on tolerability and anti-MM activity the RP2D of SRd is selinexor 60 mg QW, lenalidomide 25 mg QD and dexamethasone 40 mg QW.

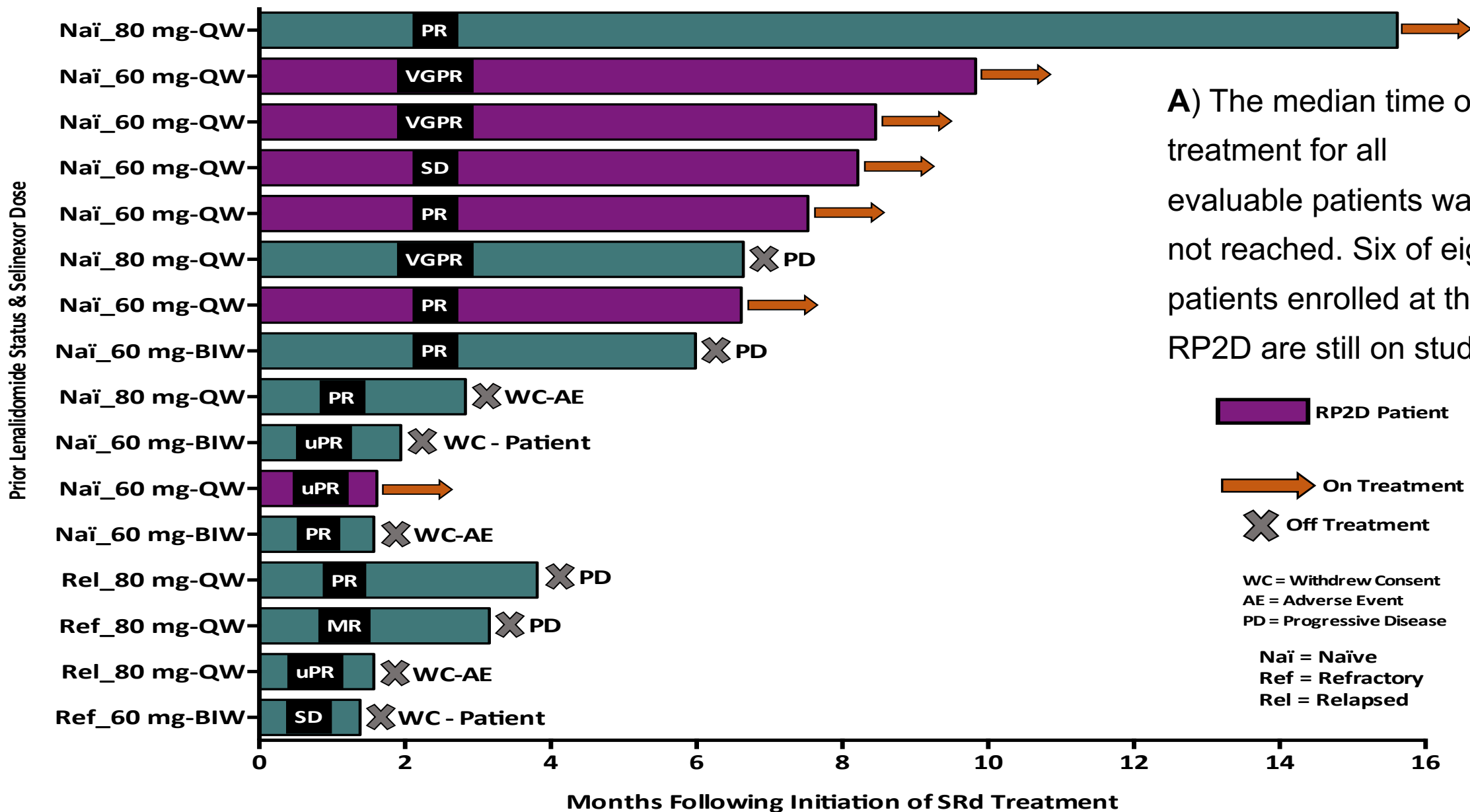
SRd Efficacy

Best Responses[†] in Evaluable SRd Patients as of November 15th, 2017

Category	N*	ORR (%)	CBR (%)	VGPR (%)	PR [‡] (%)	MR (%)	SD (%)	PD (%)
Len Naïve (all)	12	11 (92%)	11 (92%)	3 (25%)	8 (67%)	--	1 (8%)	--
Len Naïve and ≤ 2 Prior Treatment Regimens	10	10 (100%)	10 (100%)	3 (30%)	7 (70%)	--	--	--
Len Relapsed or Refractory	4	2 (50%)	3 (75%)	--	2 (50%)	1 (25%)	1 (25%)	--
All	16	13 (81%)	14 (88%)	3 (19%)	10 (63%)	1 (6%)	2 (13%)	--

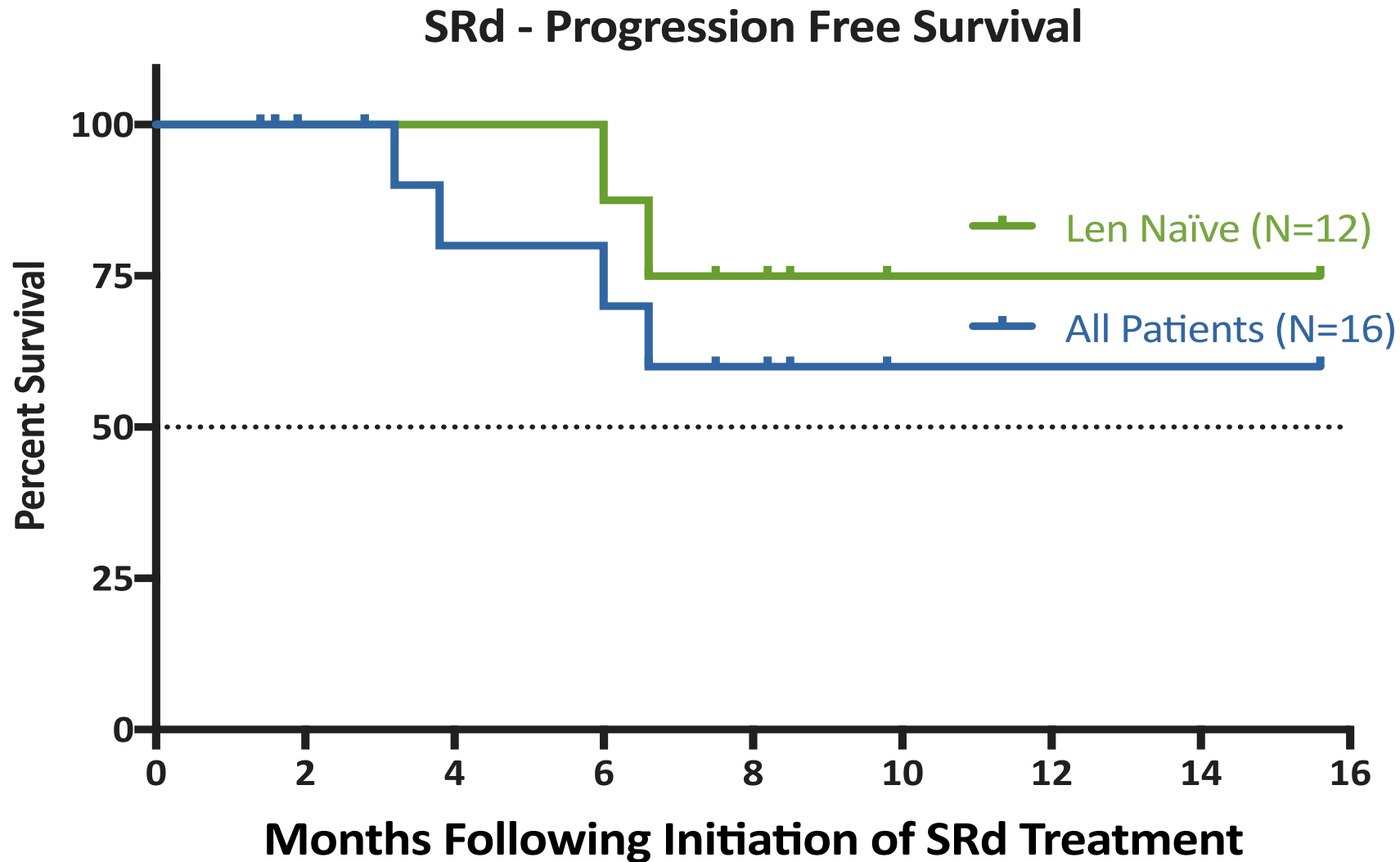
[†]Responses were adjudicated according to the *International Myeloma Working Group* criteria, **three patients not evaluable for response: two deaths unrelated to myeloma, one withdrawal of consent before disease follow up.* [‡]three unconfirmed PR. ORR=Overall Response Rate (VGPR+PR), VGPR=Very Good Partial Response, PR=Partial Response, MR=Minor Response, SD=Stable Disease, PD=Progressive Disease, CBR=Clinical Benefit Rate (ORR+MR). Responses as of November 15, 2017 based on interim unaudited data.

SRd Time on Study & Best Response



A) The median time on treatment for all evaluable patients was not reached. Six of eight patients enrolled at the RP2D are still on study.

SRd Progression Free Survival



B) Median PFS among all patients was not reached with a median follow up of 7.5 months, median PFS in lenalidomide naïve patients was not reached with a median follow up of 7.5 months.

Summary and Conclusions

- **Selinexor can be safely combined with lenalidomide (LEN) and low dose dexamethasone (SRd) in patients with heavily pretreated MM**
 - **The most common AEs are: anorexia, nausea, fatigue, mainly grades 1 and 2, neutropenia and thrombocytopenia, mainly grades 3 and 4**
- **The combination of SRd is active and encouraging with a 91% ORR in lenalidomide naïve RRMM patients**
 - **Responses occur rapidly with an ORR of 81% across all doses:**
 - **ORR of 91% in LEN-naïve patients (range 1-5 prior therapies)**
 - **ORR of 100% in LEN-naïve patients with ≤ 2 prior treatment regimens compares favorably with expected ORR of Rd of 65-75% in this population**
- **The RP2D of SRd is: selinexor 60 mg QW, lenalidomide 25 mg QD and dexamethasone 40 mg QW**
- **These results support the further studies of SRd treatment in both newly diagnosed MM patients as well as in RRMM**