Selinexor Combined with Pomalidomide and Low Dose Dexamethasone (SPd) in a Relapsed / Refractory Multiple Myeloma Patient Population

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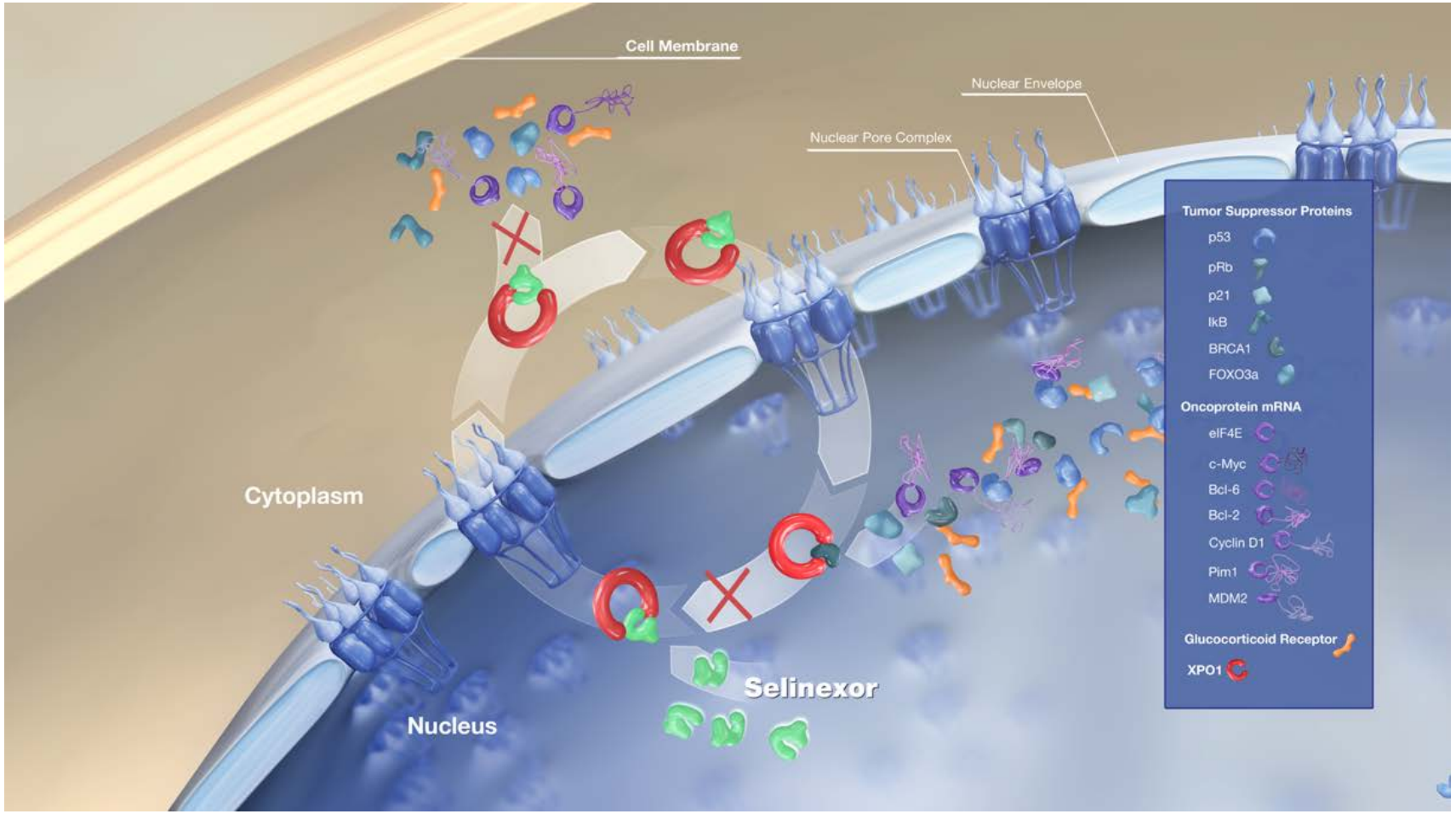
Selinexor Mechanism of Action



- 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 nuclear export (SINE) compound:
  - Reactivates multiple TSPs relevant to MM including p53, IκB and FOXO
  - Reduces c-Myc levels
  - Overcomes MDM2-mediated p53 degradation

- Selinexor has demonstrated single agent activity in patients with heavily pretreated refractory myeloma
- Selinexor reactivates p53 by increasing its protein levels, locking it in the nucleus and protecting it from MDM2-dependent-degradation
- Selinexor demonstrated synergistic activity in combination with pomalidomide and lenalidomide *in vitro* and *in vivo*

STOMP Study Design

- **S**elinexor and backbone **T**reatments **O**f multiple **M**yeloma **P**atients (**STOMP**) is an open-label, randomized (once- vs. twice-weekly dosing), dose escalation (Phase 1) and expansion (Phase 2) study in patients evaluating selinexor plus backbone therapies in patients with relapsed/refractory multiple myeloma (MM)
- **Objectives:**
  - Primary Endpoint: determine maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
  - Secondary Endpoint: determine 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 ≥ 3 thrombocytopenia with clinically significant bleeding, petechiae or purpura

STOMP Study Design (Cont.)

- **Patient Population SPd**: MM patients who received ≥ 2 prior therapies, including lenalidomide (Len) and a proteasome inhibitor (separate or same regimens) with progression during or within 60 days of last therapy; prior pomalidomide (POM) allowed
- **SPd 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. Pom dosing will be evaluated at 3 or 4 mg QD.

Drug	SVd ARM	SPd ARM	SRd ARM	SDd ARM	SKd Arm	SRd – Newly Diagnosed Patients
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	100 mg QW	60 – 80 mg, QW
Bortezomib, SC	1.3 mg/m^2 –QW/BIW	--	--	--	--	--
Pomalidomide, PO	--	3 – 4 mg, QD	--	--	--	--
Lenalidomide, PO	--	--	25 mg, QD	--	--	25 mg, QD
Daratumumab, IV	--	--	--	16 mg/kg, QW	--	--
Carfilzomib, IV	--	--	--	--	56 – 70 mg/m^2, 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	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW

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

SPd Patient Characteristics

SPd Patient Characteristics	N
Enrolled as of June 5, 2018	**34**
-60 mg selinexor BIW + 4 mg pomalidomide QD	6
-60 mg selinexor BIW + 3 mg pomalidomide QD	6
-80 mg selinexor BIW + 4 mg pomalidomide QD	6
-80 mg selinexor QW + 4 mg pomalidomide QD	7
-*80 mg selinexor QW + 3 mg pomalidomide QD	**5**
-100 mg selinexor QW + 4 mg pomalidomide QD	4
Median Age, Years (range)	61 (43 – 83)
Males : Females	16 M : 18 F
Median Years from Diagnosis to SPd Treatment, Years (range)	6 (<1 – 22)
Median Prior Regimens (range)	**4 (2 – 9)**
-Refractory to Lenalidomide	32 (94%)
-Refractory to Lenalidomide & Pomalidomide	11 (32%)
-Proteasome Inhibitor Therapy (Refractory : Exposed)	19 (56%) : 34 (100%)
-Carfilzomib Therapy	9 (26%)
-Stem Cell Transplant	27 (79%)
International Staging System (ISS) at Diagnosis	
ISS Stage I	9 (26%)
ISS Stage II	8 (24%)
ISS Stage III	7 (21%)
ISS Stage Unknown	10 (29%)

*All new patients enrolled on SPd arm, will be enrolled at this dosing regimen (80 mg QW sel, 3 mg pom)

SPd Treament Related Adverse Events ≥ 10% Patients

AE Term	60/80 mg Sel BIW + 3/4 mg Pom QD (N=18)					80/100 mg Sel QW + 3/4 mg Pom QD (N=16)				Total (N=34)
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total (N=18)**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=16)**	
Neutropenia	–	6 (33.3%)	3 (16.7%)	–	**9 (50.0%)**	2 (12.5%)	3 (18.8%)	7 (43.8%)	**12 (75.0%)**	**21 (61.7%)**
Thrombocytopenia	2 (11.1%)	3 (16.7%)	5 (27.8%)	–	**10 (55.6%)**	7 (43.8%)	2 (12.5%)	1 (6.3%)	**10 (62.5%)**	**20 (58.8%)**
Anemia	3 (16.7%)	7 (38.9%)	–	–	**10 (55.6%)**	5 (31.3%)	3 (18.8%)	--	**8 (50.0%)**	**18 (52.9%)**
Leukopenia	–	1 (5.6%)	1 (5.6%)	–	**2 (11.1%)**	4 (25.0%)	3 (18.8%)	1 (6.3%)	**8 (50.0%)**	**10 (29.4%)**
Lymphocytopenia	–	1 (5.6%)	–	–	**1 (5.6%)**	1 (6.3%)	3 (18.8%)	1 (6.3%)	**5 (31.3%)**	**6 (17.6%)**
Febrile neutropenia	–	2 (11.1%)	–	1 (5.6%)	**3 (16.7%)**	--	2 (12.5%)	--	**2 (12.5%)**	**5 (14.7%)**
Gastrointestinal										
Anorexia	11 (61.1%)	–	–	–	**11 (61.1%)**	8 (50.0%)	--	--	**8 (50.0%)**	**19 (55.9%)**
Nausea	12 (66.7%)	–	–	–	**12 (66.7%)**	4 (25.0%)	--	--	**4 (25.0%)**	**16 (47.1%)**
Diarrhea	6 (33.3%)	–	–	–	**6 (33.3%)**	3 (18.8%)	--	--	**3 (18.8%)**	**9 (26.5%)**
Altered Taste	4 (22.2%)	–	–	–	**4 (22.2%)**	4 (25.0%)	--	--	**4 (25.0%)**	**8 (23.5%)**
Vomiting	2 (11.1%)	1 (5.6%)	–	–	**3 (16.7%)**	3 (18.8%)	--	--	**3 (18.8%)**	**6 (17.6%)**
Constipation	2 (11.1%)	–	–	–	**2 (11.1%)**	2 (12.5%)	--	--	**2 (12.5%)**	**4 (11.8%)**
Constitutional										
Fatigue	9 (50.0%)	2 (11.1%)	–	–	**11 (61.1%)**	5 (31.3%)	1 (6.3%)	--	**6 (37.5%)**	**17 (50.0%)**
Weight loss	7 (38.9%)	–	–	–	**7 (38.9%)**	6 (37.5%)	--	--	**6 (37.5%)**	**13 (38.2%)**
Dehydration	5 (27.8%)	–	–	–	**5 (27.8%)**	--	--	--	**--**	**5 (14.7%)**
Weakness	2 (11.1%)	1 (5.6%)	–	–	**3 (16.7%)**	1 (6.3%)	--	--	**1 (6.3%)**	**4 (11.8%)**
Other										
Muscle spasms	3 (16.7%)	–	–	–	**3 (16.7%)**	3 (18.8%)	--	--	**3 (18.8%)**	**6 (17.6%)**
Edema	4 (22.2%)	–	–	–	**4 (22.2%)**	1 (6.3%)	--	--	**1 (6.3%)**	**5 (14.7%)**
Hyperglycemia	1 (5.6%)	1 (5.6%)	–	–	**2 (11.1%)**	3 (18.8%)	--	--	**3 (18.8%)**	**5 (14.7%)**
Hyponatremia	–	1 (5.6%)	–	–	**1 (5.6%)**	2 (12.5%)	--	1 (6.3%)	**3 (18.8%)**	**4 (11.8%)**

- Two Grade 5 related events occurred (febrile neutropenia, intracranial hemorrhage)
- Six dose limiting toxicities (DLTs) were observed (see table below)
- Doses of selinexor 60/80 mg QW and pom 3 mg are being evaluated to determine RP2D

Treatment Related Adverse Events as of June 5th, 2018

SPd DLT's

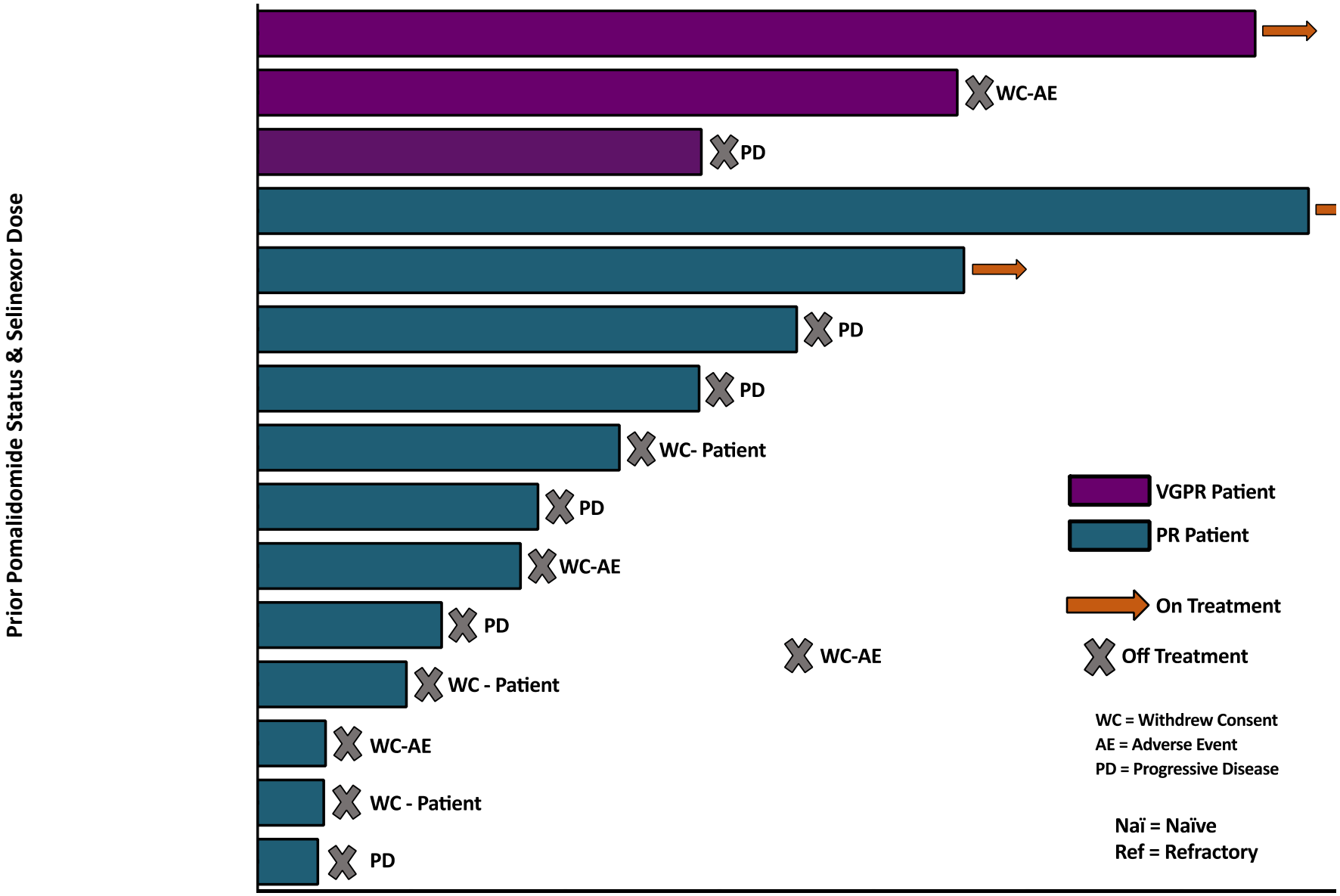
Selinexor Dose	Pomalidomide Dose	Patients Enrolled	Dose Limiting Toxicity
60 mg BIW	4 mg QD	6	• Grade 3 Fatigue
60 mg BIW	3 mg QD	6	• Grade 3 Febrile Neutropenia
80 mg BIW	4 mg QD	6	• Four (4) missed doses due to hyponatremia
100 mg QW	4 mg QD	4	• No DLT
80 mg QW	4 mg QD	7	• Grade 3 Febrile Neutropenia • Grade 4 Neutropenia
80 mg QW	3 mg QD	5	• Dose reduction for transient Grade 3 Thrombocytopenia (re-escalated and maintained at 3 mg)

SPd Efficacy

Best Responses† in Evaluable SPd Patients as of June 5th, 2018								
Category	N*	ORR (%)	CBR (%)	VGPR (%)	PR‡ (%)	MR‡ (%)	SD (%)	PD (%)
All	30	15 (50%)	19 (63%)	3 (10%)	12 (40%)	4 (13%)	11 (37%)	--
Pom Naïve & Len Refractory or Relapsed	22	12 (55%)	14 (64%)	3 (14%)	9 (41%)	2 (9%)	8 (36%)	--
Pom & Len Refractory	8	3 (38%)	5 (63%)	--	3 (38%)	2 (25%)	3 (38%)	--

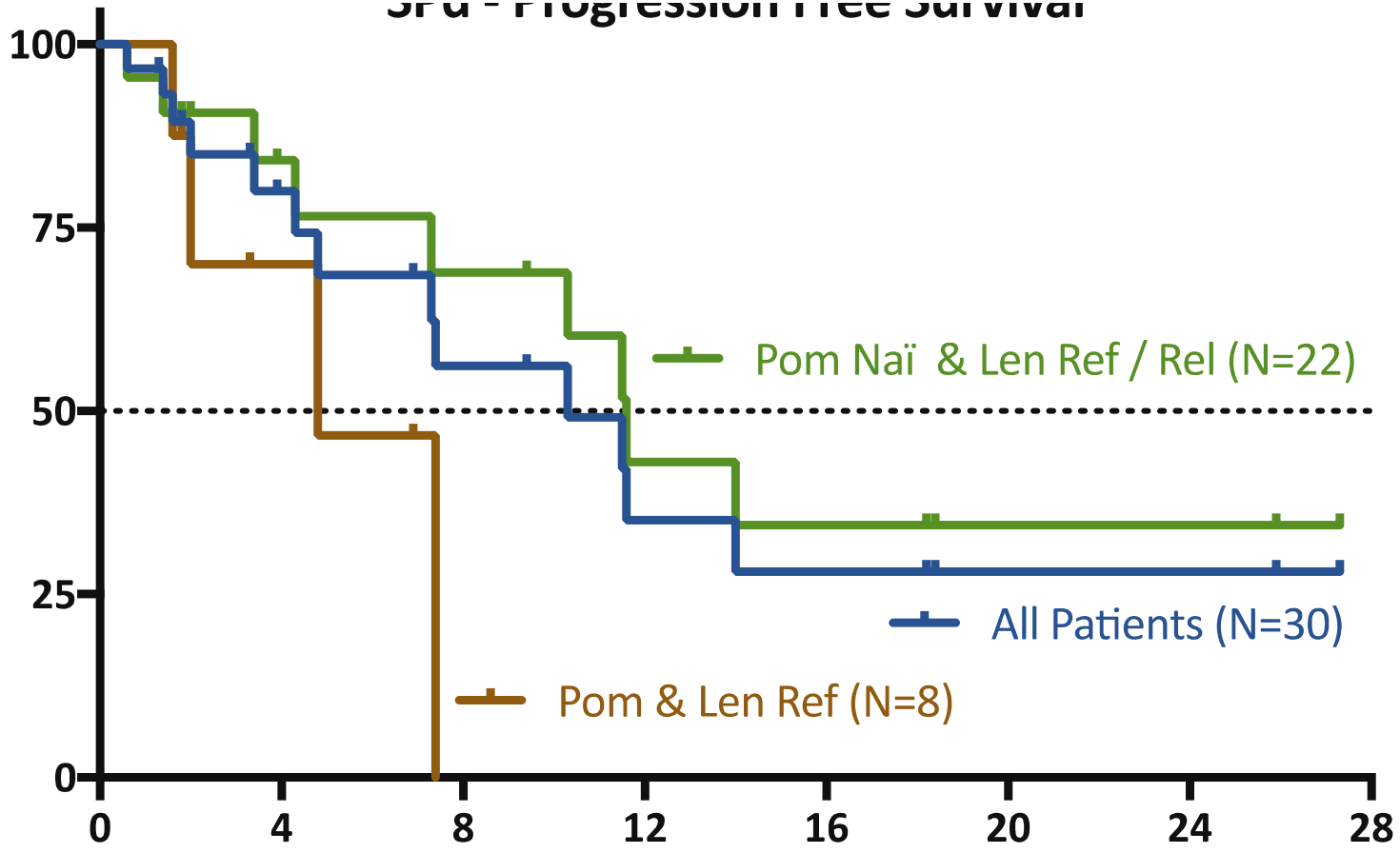
†Responses were adjudicated according to the *International Myeloma Working Group* criteria, **four patients not evaluable for response: one death unrelated to myeloma, one non-compliance with study procedures, two withdrawal of consent before disease follow up.* ‡one unconfirmed PR, one unconfirmed MR. 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 June 5th, 2018 based on interim unaudited data.

SPd Time on Study & Response, Progression Free Survival



A) Among patients with a PR or better (N=15) the median time on treatment was 9.4 months. Responses were rapid in onset with a median time to response of 1 month.

SPd Time on Study (Responders), Progression Free Survival



Patients at Risk	Months	0	2	3.4	4.8	7.3	7.4	9.4	11.6	18.2	25.9	27.3
	All Patients	30	20	17	13	11	10	9	6	4	2	1
	Pom-Naï & Len-Ref	22	15	14	11	10	--	9	6	4	2	1
	Pom & Len Ref	8	5	4	3	2	1	–	–	--	–	–

B) Median PFS among evaluable patients was 10.3 months, with a follow up of 9.4 months. Median PFS in POM-naïve and Len-refractory or relapsed MM was 11.6 months, and in POM & LEN refractory MM was 4.8 months.

Summary and Conclusions

- Selinexor, once weekly, plus pomalidomide and low-dose dexamethasone (SPd) is being evaluated in an ongoing phase 1 study 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 (bleeding was uncommon)
  - Determination of the recommended phase 2 dose of SPd is ongoing with with once-weekly selinexor and pomalidomide once-daily
- The combination of SPd appears active and durable, and responses typically occur within 1 cycle of treatment
  - ORR of 55% in pomalidomide-naïve patients (compared to expected ORR of ≤ 30% of pomalidomide + dex based on pomalidomide approval)
  - ORR 50% across all doses
  - PFS in pomalidomide-naïve patients 11.6 months (compared to expected PFS of ~4 months for pomalidomide + dex)