Selinexor in Combination with Pomalidomide and Low Dose Dexamethasone (SPd) in a Relapsed / Refractory Multiple Myeloma Patient Population with Prior Proteasome Inhibitor and Lenalidomide Exposure

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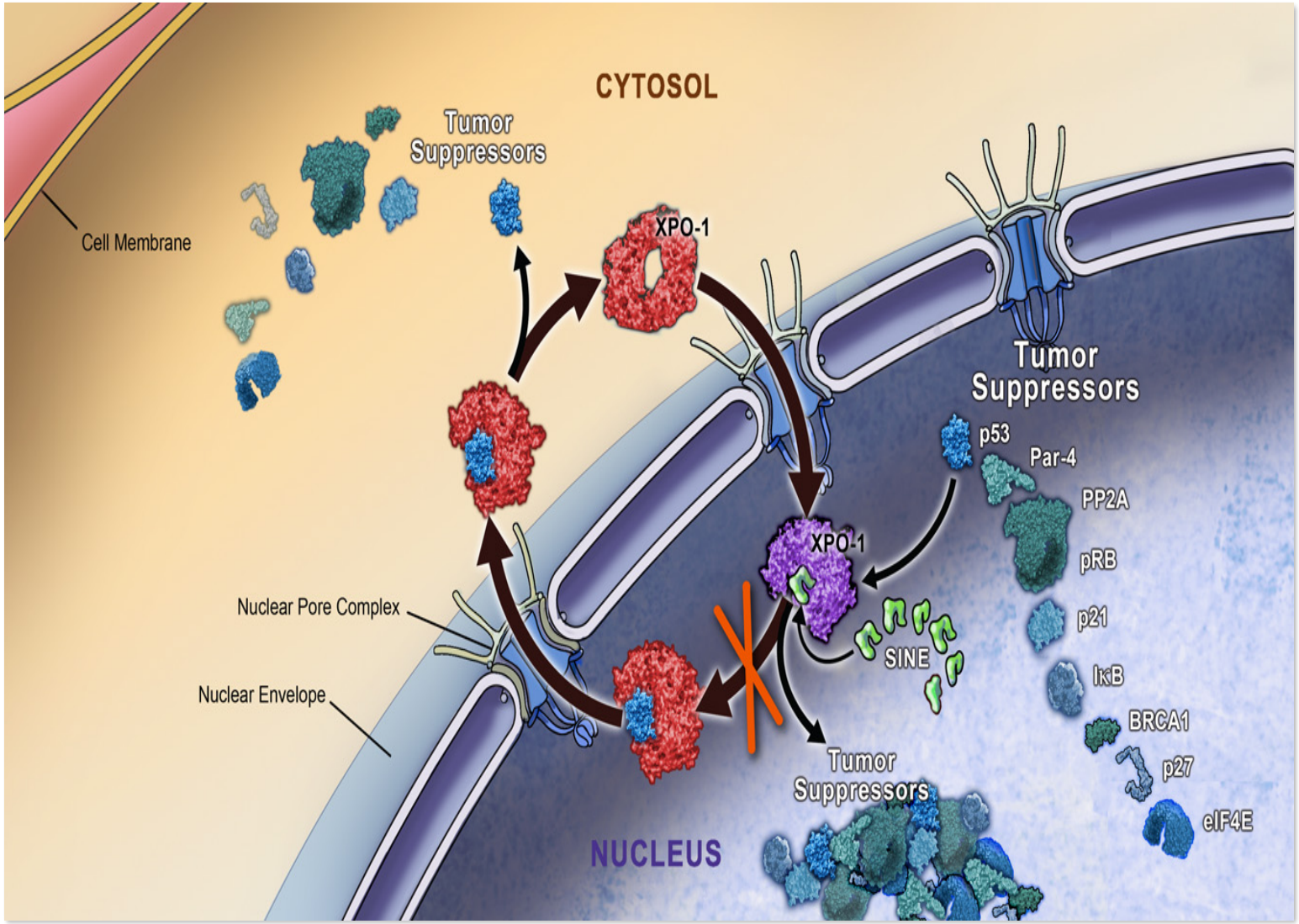
Selinexor Mechanism of Action



- 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

- **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 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 ≥ 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
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 SPd arm. BIW=Twice Weekly, QW=Once Weekly, Dexamethasone will be dosed on selinexor dosing days

SPd Patient Characteristics

SPd Patient Characteristics	N
Patients Enrolled as of November 1, 2017	**31**
-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	2
-100 mg selinexor QW + 4 mg pomalidomide QD	4
Median Age, Years (range)	61 (43 – 83)
Males : Females	15 M : 16 F
Median Years from Diagnosis to SPd Treatment, Years (range)	6 (<1 – 22)
Median Prior Regimens (range)	**4 (2 – 9)**
-Refractory to Prior Lenalidomide Therapy	29 (94%)
-Refractory to Prior Lenalidomide & Pomalidomide Therapy	11 (35%)
-Prior Proteasome Inhibitor Therapy (Refractory : Exposed)	18 (58%) : 31 (100%)
-Prior Carfilzomib Therapy	9 (29%)
-Prior Stem Cell Transplant	24 (77%)
ISS at Diagnosis	
ISS I	7 (23%)
ISS II	6 (19%)
ISS III	5 (16%)
Unknown	8 (26%)

SPd Related Adverse Events ≥ 3 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=13)				Total (N=31)
Gastrointestinal	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total**	
Nausea	12 (66.7%)	--	--	--	**12 (66.7%)**	4 (30.8%)	--	--	**4 (30.8%)**	**16 (51.6%)**
Anorexia	10 (55.6%)	--	--	--	**10 (55.6%)**	4 (30.8%)	--	--	**4 (30.8%)**	**14 (45.2%)**
Diarrhea	7 (38.9%)	--	--	--	**7 (38.9%)**	3 (23.1%)	--	--	**3 (23.1%)**	**10 (32.3%)**
Vomiting	2 (11.1%)	1 (5.6%)	--	--	**3 (16.7%)**	4 (30.8%)	--	--	**4 (30.8%)**	**7 (22.6%)**
Altered Taste	4 (22.2%)	--	--	--	**4 (22.2%)**	3 (23.1%)	--	--	**3 (23.1%)**	**7 (22.6%)**
Constipation	2 (11.1%)	--	--	--	**2 (11.1%)**	2 (15.4%)	--	--	**2 (15.4%)**	**4 (12.9%)**
Stomatitis	2 (11.1%)	--	--	--	**2 (11.1%)**	1 (7.7%)	--	--	**1 (7.7%)**	**3 (9.7%)**
Constitutional										
Fatigue	9 (50.0%)	2 (11.1%)	--	--	**11 (61.1%)**	5 (38.5%)	--	--	**5 (38.5%)**	**16 (51.6%)**
Weight Loss	4 (22.2%)	--	--	--	**4 (22.2%)**	5 (38.5%)	--	--	**5 (38.5%)**	**9 (29.0%)**
Dehydration	5 (27.8%)	--	--	--	**5 (27.8%)**	--	--	--	--	**5 (16.1%)**
Hematologic										
Neutropenia	--	7 (38.9%)	2 (11.1%)	--	**9 (50.0%)**	1 (7.7%)	2 (15.4%)	6 (46.2%)	**9 (69.2%)**	**18 (58.1%)**
Thrombocytopenia	1 (5.6%)	4 (22.2%)	4 (22.2%)	--	**9 (50.0%)**	5 (38.5%)	1 (7.7%)	1 (7.7%)	**7 (53.8%)**	**16 (51.6%)**
Anemia	3 (16.7%)	7 (38.9%)	--	--	**10 (55.6%)**	2 (15.4%)	2 (15.4%)	--	**4 (30.8%)**	**14 (45.2%)**
Leukopenia	--	1 (5.6%)	1 (5.6%)	--	**2 (11.1%)**	1 (7.7%)	2 (15.4%)	1 (7.7%)	**4 (30.8%)**	**6 (19.4%)**
Febrile Neutropenia	--	2 (11.1%)	--	1 (5.6%)	**3 (16.7%)**	--	2 (15.4%)	--	**2 (15.4%)**	**5 (16.1%)**
Lymphopenia	--	1 (5.6%)	--	--	**1 (5.6%)**	1 (7.7%)	1 (7.7%)	1 (7.7%)	**3 (23.1%)**	**4 (12.9%)**
Other										
Muscle spasms	3 (16.7%)	--	--	--	**3 (16.7%)**	3 (23.1%)	--	--	**3 (23.1%)**	**6 (19.4%)**
Peripheral Edema	4 (22.2%)	--	--	--	**4 (22.2%)**	--	--	--	--	**4 (12.9%)**
Hyperglycaemia	1 (5.6%)	1 (5.6%)	--	--	**2 (11.1%)**	2 (15.4%)	--	--	**2 (15.4%)**	**4 (12.9%)**
Dizziness	2 (11.1%)	--	--	--	**2 (11.1%)**	2 (15.4%)	--	--	**2 (15.4%)**	**4 (12.9%)**
Vision Blurred	1 (5.6%)	--	--	--	**1 (5.6%)**	2 (15.4%)	--	--	**2 (15.4%)**	**3 (9.7%)**
Dry Skin	1 (5.6%)	--	--	--	**1 (5.6%)**	2 (15.4%)	--	--	**2 (15.4%)**	**3 (9.7%)**
Insomnia	2 (11.1%)	--	--	--	**2 (11.1%)**	1 (7.7%)	--	--	**1 (7.7%)**	**3 (9.7%)**
Pneumonia	--	1 (5.6%)	--	--	**1 (5.6%)**	2 (15.4%)	--	--	**2 (15.4%)**	**3 (9.7%)**
Hypoalbuminaemia	--	--	--	--	**--**	3 (23.1%)	--	--	**3 (23.1%)**	**3 (9.7%)**
Hypokalemia	--	1 (5.6%)	--	--	**1 (5.6%)**	2 (15.4%)	--	--	**2 (15.4%)**	**3 (9.7%)**
Hyponatremia	--	1 (5.6%)	--	--	**1 (5.6%)**	1 (7.7%)	--	1 (7.7%)	**2 (15.4%)**	**3 (9.7%)**

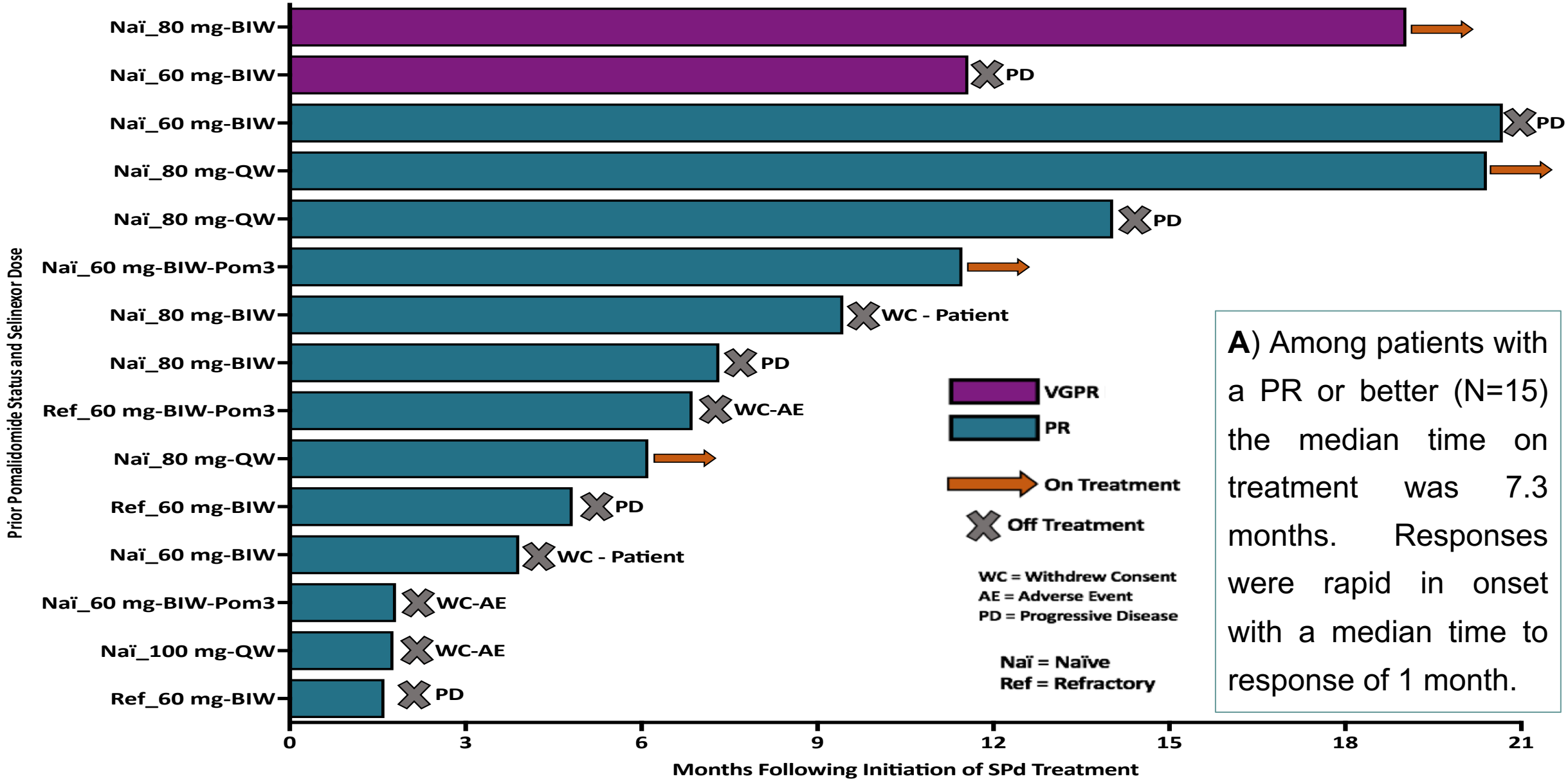
Related Adverse Events SPd Patients: The most common adverse events include: nausea, anorexia, fatigue, (mainly G1/2) neutropenia and thrombocytopenia (mainly G3/4). GI adverse events were generally manageable with antiemetics. Two Grade 5 related events occurred (febrile neutropenia, intracranial hem-orrhage). Five dose limiting toxicities (DLTs) were observed: G3 fatigue (60 mg BIW, pom 4 mg), G3 febrile neutropenia (60 mg BIW, pom 3 mg), G3 febrile neutropenia (80 mg QW, pom 4), G4 neutropenia (80 mg QW, pom 4), and 4 missed doses in Cycle 1 due to symptomatic hyponatremia (80 mg BIW, pom 4 mg). Doses of selinexor 60/80 mg QW and and pom 3 mg are being evaluated to determine RP2D.

SPd Efficacy

Best Responses† in Evaluable SPd Patients as of November 15th, 2017								
Category	**N***	**ORR (%)**	**CBR (%)**	**VGPR (%)**	**PR‡ (%)**	**MR‡ (%)**	**SD (%)**	**PD (%)**
All	27	**15 (56%)**	**19 (70%)**	2 (7%)	13 (48%)	4 (15%)	8 (30%)	--
Pom Naïve & Len Refractory or Relapsed	19	**12 (63%)**	**14 (74%)**	2 (11%)	10 (53%)	2 (11%)	5 (26%)	--
Pom & Len Refractory	8	**3 (38%)**	**5 (63%)**	--	3 (38%)	2 (25%)	3 (38%)	--

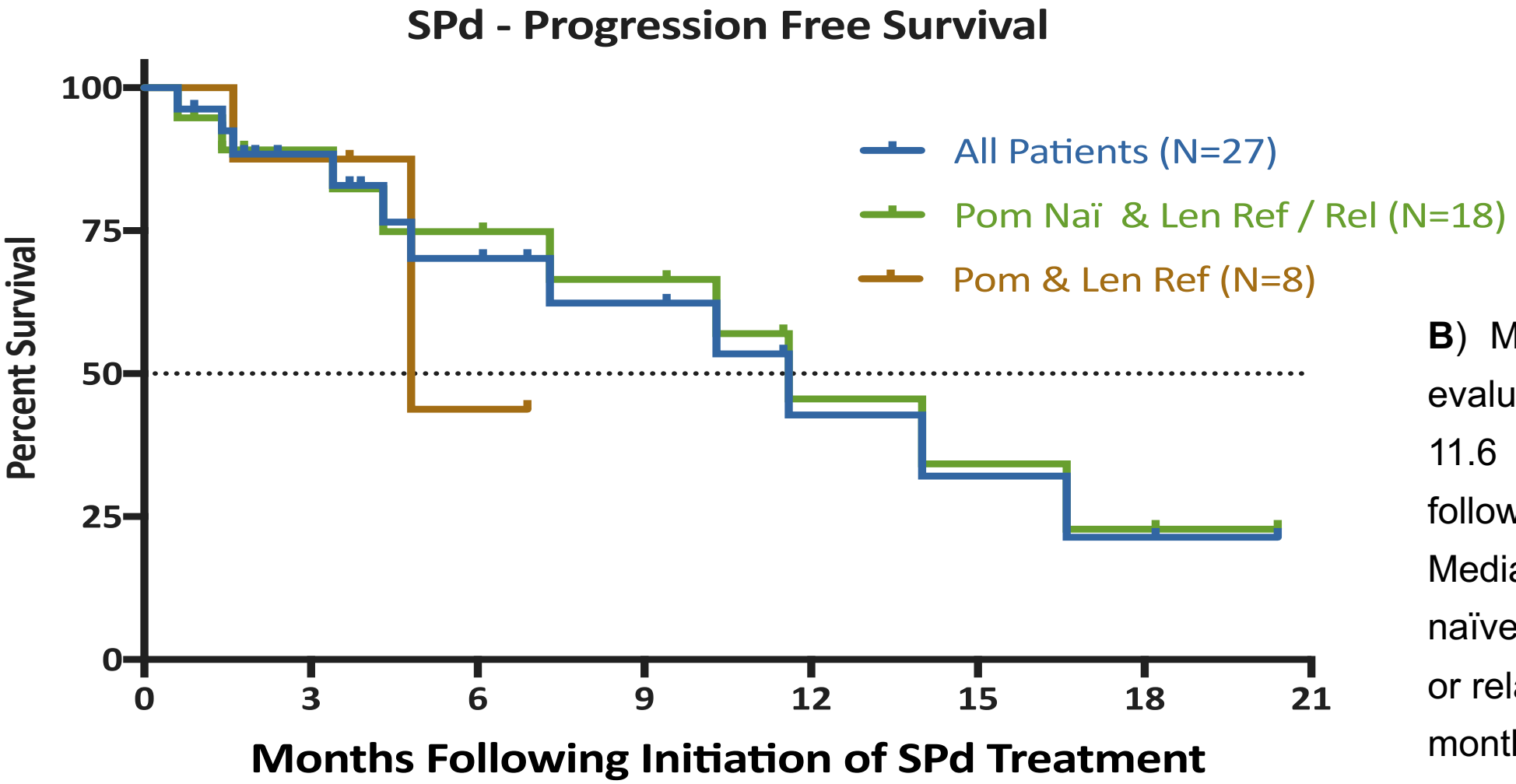
†Responses were adjudicated according to the *International Myeloma Working Group* criteria, **four patients not evaluable for response: one death unrelated to myeloma, one non-compliance with study procedures, two withdrawal of consent before disease follow up.* ‡one unconfirmed PR, one unconfirmed 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 November 15, 2017 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 7.3 months. Responses were rapid in onset with a median time to response of 1 month.

SPd Time on Study (Responders), Progression Free Survival



B) Median PFS among evaluable patients was 11.6 months, with a follow up of 7 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, combined with pomalidomide (POM) and low dose dexamethasone (SPd) is being evaluated in an ongoing phase I 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 combination dose of SPd is ongoing with POM QD with once-weekly selinexor
- The combination of SPd is active, durable, and responses are rapid typically occurring within 1 cycle of treatment:
  - ORR of 63% in POM naïve patients (expected ORR of Pd is ≤30% based on Pd approval)
  - ORR 56% overall across all doses
  - PFS in POM naïve patients 11.6 months (expected PFS of Pd is ~4 months)
- The novel all-oral SPd combination is generally well tolerated and can rapidly induce durable responses in patients with PI and LEN-refractory MM