Selinexor Shows Synergy in Combination with Pomalidomide and Low Dose Dexamethasone in Patients with Relapsed / Refractory Multiple Myeloma: Phase I STOMP Trial

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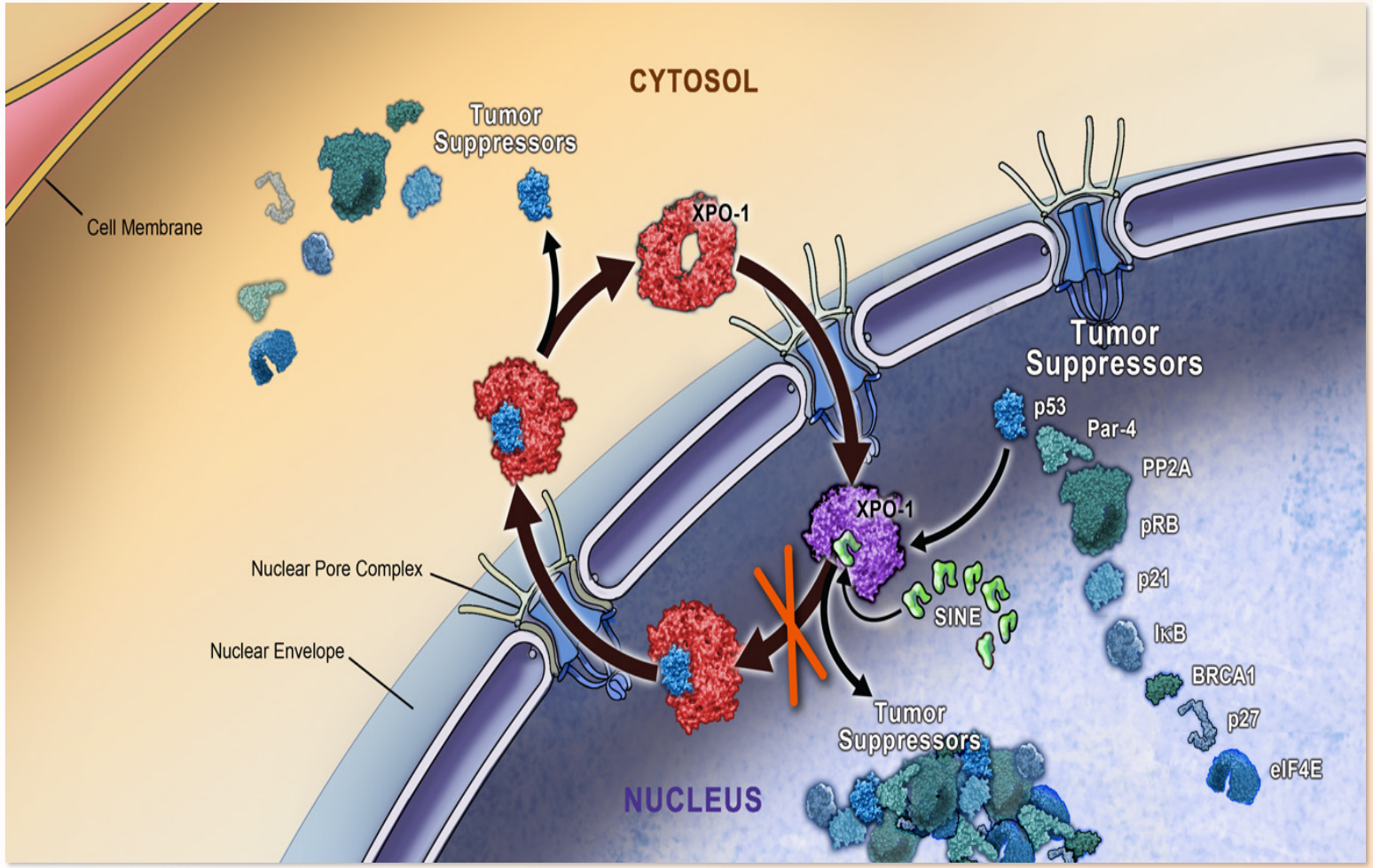
Selinexor Mechanism of Action



- 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)
- XPO1 is overexpressed in MM and other hematological malignancies and its levels often correlate with poor prognosis
- Selinexor, a 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), with dose escalation (Phase I) and expansion (Phase II) combination study in patients with relapsed/refractory multiple myeloma
  - **ARM SPd** – Selinexor + dexamethasone + pomalidomide: ~28 patients (dose escalation)
  - **ARM SVd** – Selinexor + dexamethasone + bortezomib: ~28 patients (dose escalation)
  - **ARM SLd** – Selinexor + dexamethasone + lenalidomide: ~28 patients (dose escalation)
- **Objectives:**
  - Primary: maximum tolerated dose (MTD) and recommended Phase II dose (RP2D)
  - Secondary: overall response rate (ORR) and duration of response (DOR) for each arm independently
- **Dose Limiting Toxicity (DLT) Definitions:**
  - >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

THE DATA PRESENTED WILL FOCUS ON PATIENTS ENROLLED ON THE SPd ARM

SPd Patient Population & Dosing Schemes

- **Patient Population SPd**:
  - **Arm SPd:** MM patients who received ≥ 2 prior therapies, including lenalidomide and a proteasome inhibitor (separate or same regimens) with progression during or within 60 days of completion of last therapy
- **Phase I Dose Escalation Treatment Scheme:** A standard 3 + 3 design will be used for all dose escalations for each arm independently. Once the MTD in a cohort is reached, additional patients will be added to each cohort to achieve a target of 17 evaluable patients who have been treated at that MTD for that cohort. Dosing schemes can be seen below:

Drug	Selinexor Once Weekly	Selinexor Twice Weekly
Selinexor, oral QW/BIW	Dose Level 1 : 80 mg Dose Level 2 : 100 mg	Dose Level 1 : 60 mg Dose Level 2 : 80 mg
Pomalidomide, oral, QD x 21 d	4 m g	4 mg
Dexamethasone, oral QW/BIW	40 mg QW	20 mg BIW

BIW=Twice Weekly, QW=Once Weekly, Dexamethasone will be dosed on selinexor dosing days

SPd Patient Characteristics

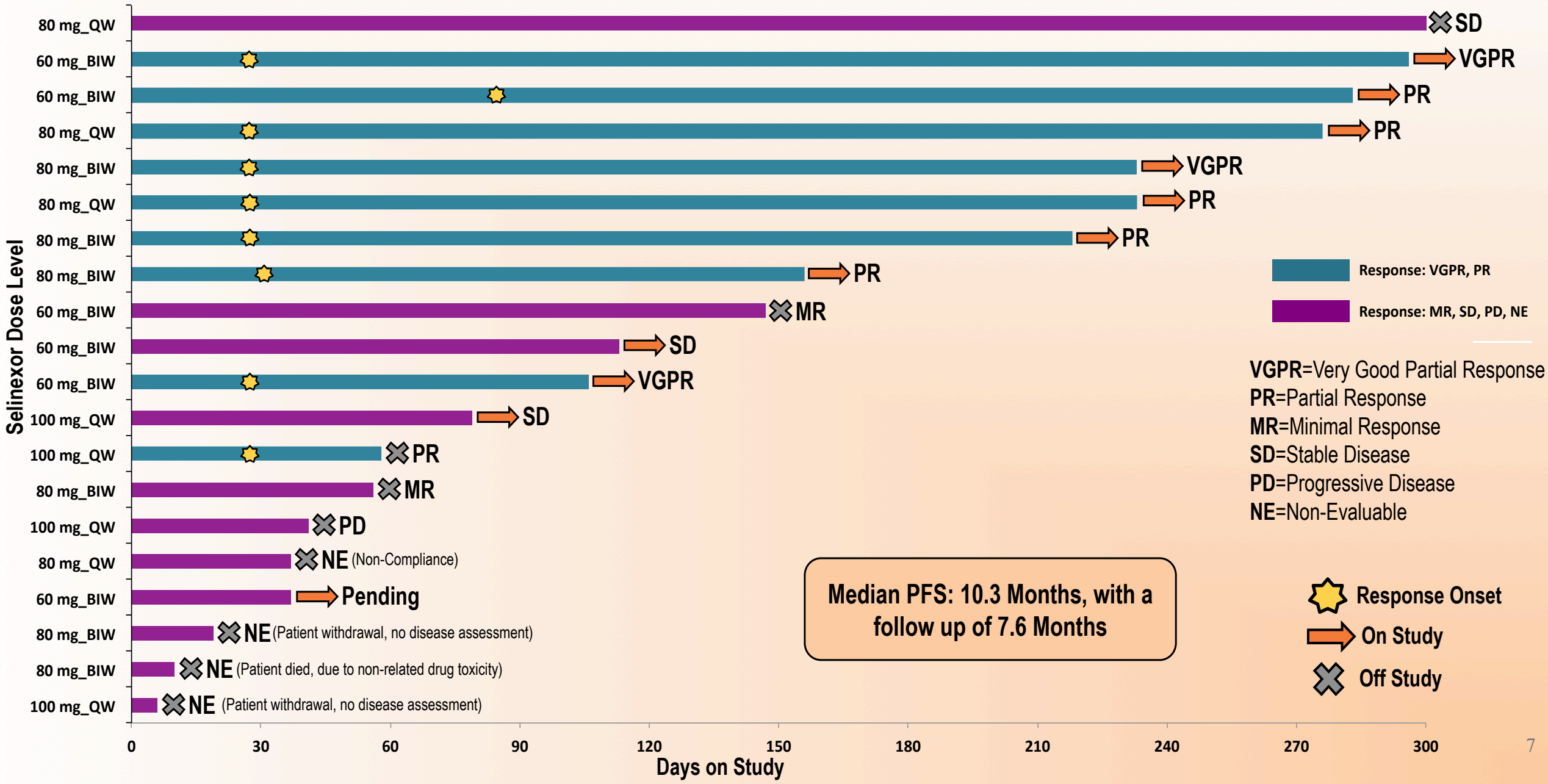
SPd Patient Characteristics	N
Patients Enrolled as of November 1, 2016	**20**
Median Age, Years (range)	61 (43 – 83)
Males : Females	10 M : 10 F
High Risk Cytogenetics (del17p, t (4;14))	5 (25%)
Median Prior Regimens (range) -Prior Lenalidomide -Prior Proteasome Inhibitor	**5 (2 – 9)** 20 (100%) 20 (100%)
ISS at Diagnosis ISS I ISS II ISS III Unknown	 4 (20%) 5 (25%) 2 (10%) 9 (45%)

SPd Related Adverse Events

AE Term	60 mg Sel BIW + 4 mg POM Daily N=6				80 mg Sel BIW + 4 mg POM Daily N=6				80 mg Sel QW + 4 mg POM Daily N=4				100 mg Sel QW + 4 mg POM Daily N=4			
Gastrointestinal	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total**
Anorexia	4 (67%)	--	--	**4 (67%)**	2 (33%)	--	--	**2 (33%)**	1 (25%)	--	--	**1 (25%)**	1 (25%)	--	--	**1 (25%)**
Nausea	5 (83%)	--	--	**5 (83%)**	3 (50%)	--	--	**3 (50%)**	2 (50%)	--	--	**2 (50%)**	2 (50%)	--	--	**2 (50%)**
Altered Taste	2 (33%)	--	--	**2 (33%)**	1 (17%)	--	--	**1 (17%)**	2 (50%)	--	--	**2 (50%)**	--	--	--	**--**
Dehydration	2 (33%)	--	--	**2 (33%)**	2 (33%)	--	--	**2 (33%)**	--	--	--	**--**	--	--	--	**--**
Constitutional																
Fatigue	1 (17%)	1 (17%)	--	**2 (33%)**	3 (50%)	--	--	**3 (50%)**	1 (25%)	--	--	**1 (25%)**	2 (50%)	--	--	**2 (50%)**
Blood																
Thrombocytopenia	1 (17%)	3 (50%)	1 (17%)	**5 (83%)**	--	2 (33%)	--	**2 (33%)**	3 (75%)	--	--	**3 (75%)**	--	--	--	**--**
Neutropenia	--	3 (50%)	1 (17%)	**4 (67%)**	--	3 (50%)	--	**3 (50%)**	--	2 (50%)	1 (25%)	**3 (75%)**	--	--	1 (25%)	**1 (25%)**
Anemia	--	2 (33%)	--	**2 (33%)**	1 (17%)	1 (17%)	--	**2 (33%)**	--	--	--	**--**	1 (25%)	--	--	**1 (25%)**

Related Adverse Events SPd Patients: The most common adverse events include: anorexia, nausea, fatigue, and thrombocytopenia. GI toxicities were generally manageable with antiemetics, no febrile neutropenia or bleeding has been observed. There has been 1 DLT reported: Grade 3 fatigue (60 mg BIW selinexor).

SPd Cohort, Time on Study & Response



SPd Efficacy

Best Responses† in Evaluable SPd Patients as of November 28, 2016								
Category	**N**	**ORR (%)**	**CBR (%)**	**VGPR (%)**	**PR‡ (%)**	**MR (%)**	**SD (%)**	**PD (%)**
All Patients	15	**9 (60%)**	11 (73%)	3 (20%)	6 (40%)	2 (13%)	3 (20%)	1 (7%)

†Responses were adjudicated according to the *International Myeloma Working Group* criteria, ‡one 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 (VGPR+PR+MR).
Responses as of November 28, 2016 based on interim unaudited data.

Summary & Conclusions

- Selinexor can be safely combined with pomalidomide and low dose dexamethasone (SPd) in patients with heavily pretreated MM
- The most common AEs are: anorexia, nausea, fatigue, and thrombocytopenia, mainly grades 1 and 2, similar to selinexor or pomalidomide used separately
- Even with dose escalations continuing, responses seen with SPd are encouraging and occur within a median of 1 cycle of treatment
  - ORR 60% overall across doses
  - In this population, pomalidomide + low dex has an expected ORR of ~30%
- Determination of the recommended combination dose of SPd is ongoing, evaluating pomalidomide 3 mg po qd with weekly selinexor 100 mg to reduce cytopenias
- This all-oral SPd combination is generally well tolerated and can rapidly induce durable responses in patients with heavily pretreated MM