A Phase 1B/2 Study of Selinexor in Combination with Backbone Therapies for Treatment of Relapsed/Refractory Multiple Myeloma

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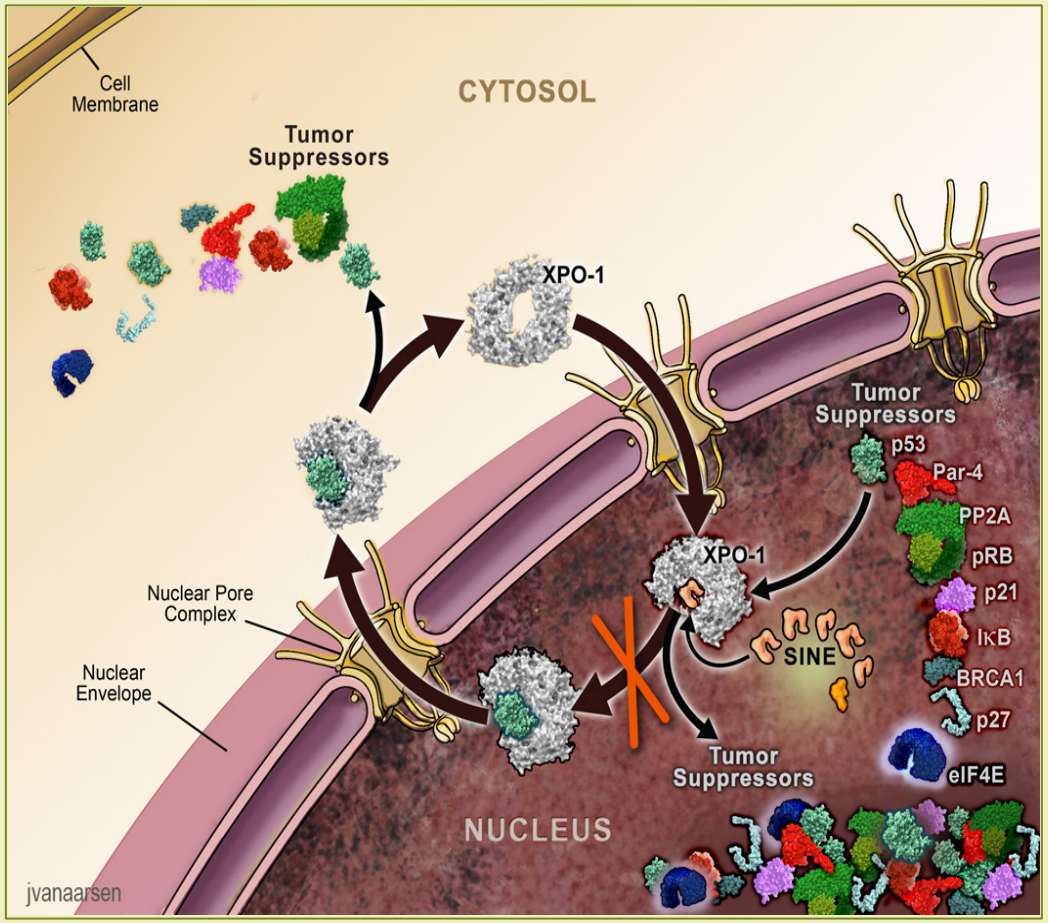
Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs) and eIF4E-bound oncoprotein mRNAs (c-myc,BCL2, BCL-xL and cyclins)
- XPO1 is overexpressed in MM and other hematological malignancies and its levels often correlate with poor prognosis
- **MM is a Rational Indication for Selinexor:**
- Selinexor reactivates multiple TSPs relevant to MM including p53, IκB and FOXO, and overcomes MDM2-mediated p53 degradation
- Selinexor increases IκB, which inhibits hyperactive NF-κB commonly found in MM
- By trapping mRNAs bound to eIF4E, selinexor reduces expression of c-myc, BCL2, cyclin D, MDM2 and survivin – oncoproteins that are frequently overexpressed in MM

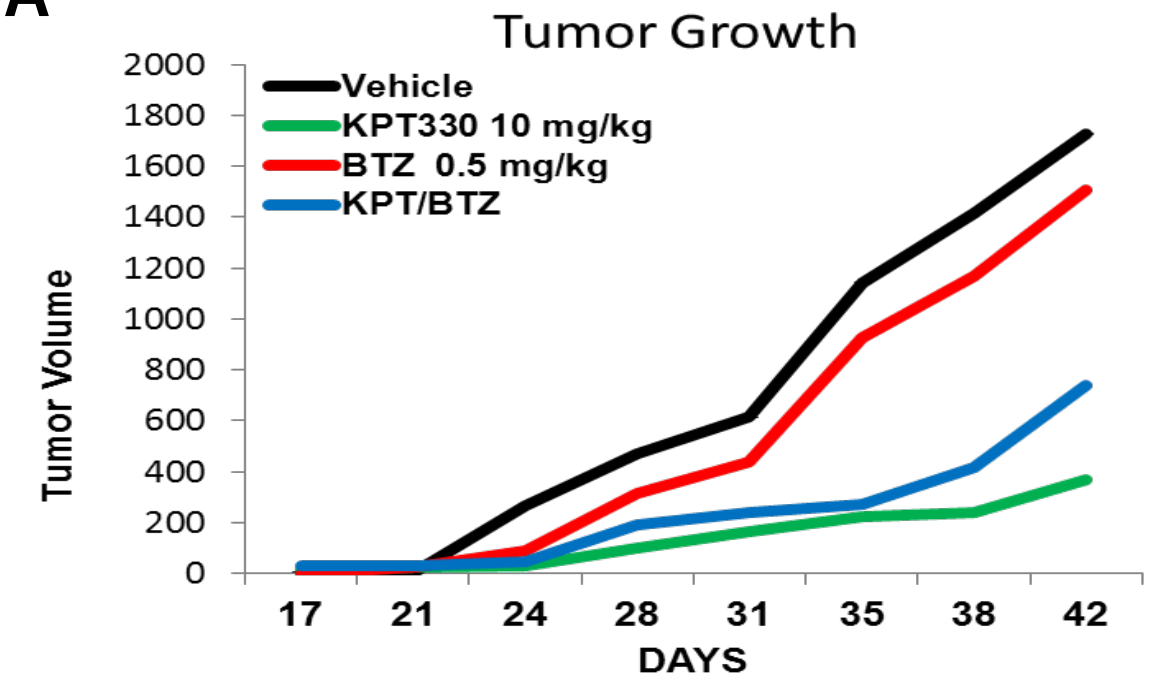
- Inhibition of XPO1 by selinexor also induces a perturbation in the ribosome subunits transfer, disruption of ribosomal assembly and the induction of a ribosomal stress response in MM cells
- Selinexor has demonstrated single agent activity in patients with heavily pretreated refractory myeloma

Selinexor Combinations: Mechanism of Action

- **Rationale for combining selinexor with Proteasome Inhibitors**:
- In preclinical models of MM selinexor synergizes with bortezomib and carfilzomib through repression of NF-κB pathway and induction of autophagy in MM
- In a clinical study in patients with MM, the proteasome inhibitor carfilzomib in combination with selinexor shows promising clinical activity (Jakubowiak, ASH 2015)
- **Rationale for combining selinexor with IMiDs:**
- Selinexor demonstrated synergistic activity in combination with pomalidomide and lenalidomide in vitro and in vivo

Pre-Clinical Activity

A



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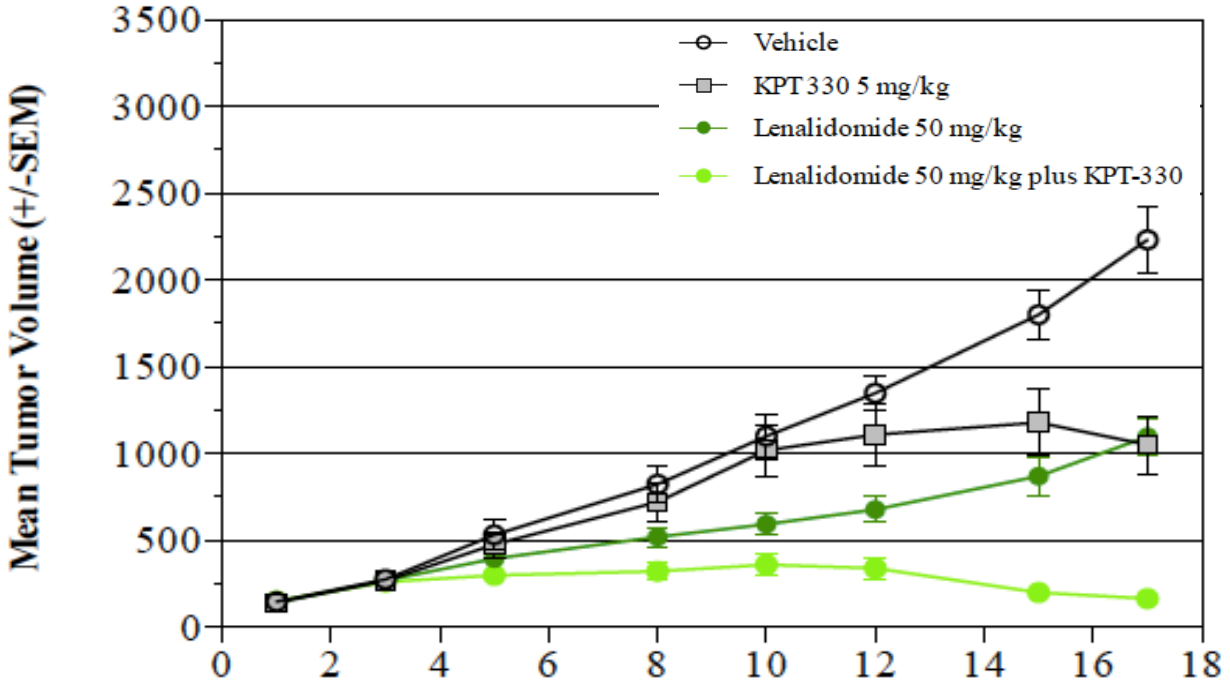


Selinexor in Combination with Bortezomib or Lenalidomide is Synergistic in MM *In-Vivo*: **(A)** In a MM xenograft (bortezomib/doxorubicin resistant), the combination of selinexor and bortezomib reduced tumor growth *(Turner, AACR 2014)* **(B)** In a MM xenograft (MM.1S), the combination of selinexor + lenalidomide reduced tumor growth as compared to selinexor or lenalidomide treatment alone

STOMP Phase 1b/2 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 selinexor dosing), with dose escalation (Phase I) and expansion (Phase II) combination study in patients with relapsed/refractory multiple myeloma
  - **ARM SdB** – Selinexor + dexamethasone + bortezomib: up to ~28 patients (dose escalation)
  - **ARM SdP** – Selinexor + dexamethasone + pomalidomide: up to ~28 patients (dose escalation)
  - **ARM SdL** – Selinexor + dexamethasone + lenalidomide: up to ~28 patients (dose escalation)
- **Primary Objectives Phase I: ARMs SdB, SdP, SdL**
  - Determine the maximum tolerated dose (MTD) for selinexor in combination with bortezomib, pomalidomide, and lenalidomide independently
  - Determine the recommended Phase II dose (RP2D) for each arm independently
- **Primary Objectives Phase II: ARMs SdB, SdP, SdL**
  - Determine the overall response rate (ORR) for each arm independently
  - Determine the 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

Patient Population & Dose Escalation

- **Patient Populations by ARM**:
  - **Arm SdB:** MM patients relapsing after ≥ 1 prior therapy may include prior bortezomib, provided MM was not refractory to prior bortezomib as the last prior therapy
  - **Arm SdP:** MM patients after ≥ 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
  - **Arm SdL:** MM patients relapsing after ≥ 1 prior therapy that may include prior lenalidomide, provided MM was not refractory to prior lenalidomide as the last prior 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 and current cohort enrollment are seen below.

STOMP Patient Characteristics, Cohorts, & Dosing Scheme

Characteristic	ARM: SdB N=16	ARM: SdP N=10	ARM: SdL N=2
Median Age (Range)	67.5 (46 – 74)	57 (43 – 76)	70.5 (57 – 84)
Male : Female	8 : 8	7 : 3	2 : 0
Median Prior Treatment Regimens (Range)	5 (1 – 12)	5 (2 – 9)	1 (1 – 2)
ISS at Diagnosis (I : II : III : Unk)	6 : 4 : 4 : 2	3 : 3 : 2 : 2	0 : 1 : 0 : 1
High Risk Cytogenetics, FISH (%)	13%	20%	0%

Combination Drug & Dose	Selinexor Dose* / Patients Enrolled			
	60 mg BIW	80 mg BIW	80 mg QW	100 mg QW
Bortezomib 1.3 mg/m^2 QW	3	3	4	3
Bortezomib 1.3 mg/m^2 BIW	--	--	3	--
Pomalidomide Daily 4 mg 21 Days	3	3	4	--
Lenalidomide Daily 25 mg 21 Days	1	--	1	--

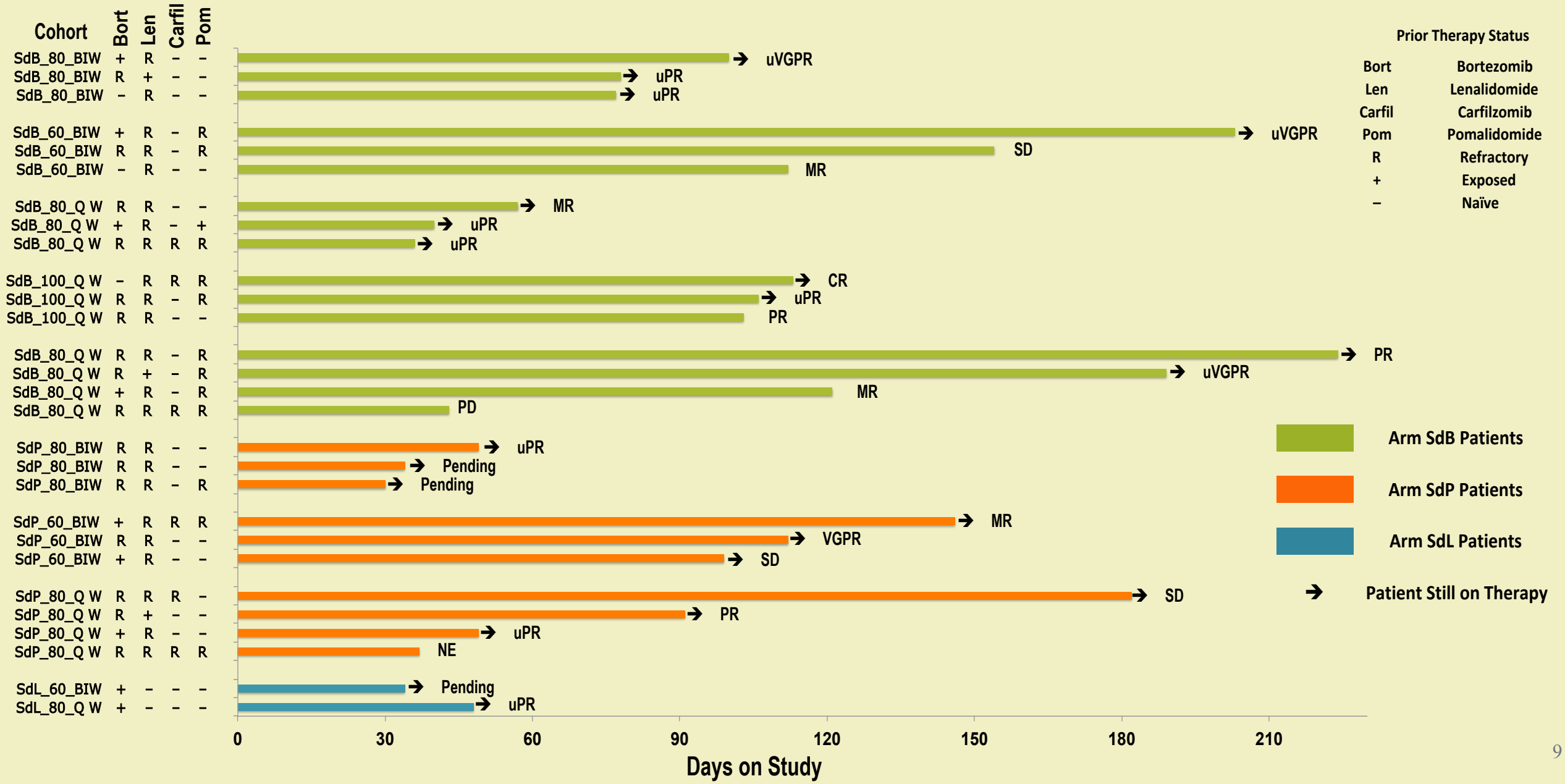
*QW=Once Weekly, BIW=Bi-Weekly, Dexamethasone will be dosed on selinexor dosing days at 20 mg BIW or 40 mg QW

Related Adverse Events: ARMs SdB, SdP, SdL

AE Term	Selinexor + Bortezomib + Dexamethasone (N=16)					Selinexor + Pomalidomide + Dexamethasone (N=10)					Selinexor + Lenalidomide + Dexamethasone (N=2)			
Gastrointestinal	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
Anorexia	3 (18.8%)	2 (12.5%)	--	--	**5 (31.3%)**	--	1 (10.0%)	--	--	**1 (10.0%)**	1 (50.0%)	--	1 (50.0%)	**2 (100%)**
Nausea	3 (18.8%)	1 (6.3%)	--	--	**4 (25.0%)**	3 (30.0%)	2 (20.0%)	--	--	**5 (50.0%)**	--	1 (50.0%)	--	**1 (50.0%)**
Diarrhea	1 (6.3%)	1 (6.3%)	1 (6.3%)	--	**3 (18.8%)**	2 (20.0%)	--	--	--	**2 (20.0%)**	--	--	--	**--**
Dysgeusia	1 (6.3%)	1 (6.3%)	--	--	**2 (12.5%)**	3 (30.0%)	1 (10.0%)	--	--	**4 (40.0%)**	--	--	--	**--**
Constipation	2 (12.5%)	--	--	--	**2 (12.5%)**	1 (10.0%)	--	--	--	**1 (10.0%)**	1 (50.0%)	1 (50.0%)	--	**2 (100%)**
Vomiting	--	2 (12.5%)	--	--	**2 (12.5%)**	--	--	--	--	**--**	--	--	--	**--**
Constitutional														
Fatigue	2 (12.5%)	4 (25.0%)	1 (6.3%)	--	**7 (43.8%)**	--	3 (30.0%)	--	--	**3 (30.0%)**	--	1 (50.0%)	--	**1 (50.0%)**
Weight loss	1 (6.3%)	2 (12.5%)	--	--	**3 (18.8%)**	--	--	--	--	**--**	--	--	--	**--**
Blood														
Thrombocytopenia	--	--	4 (25.0%)	2 (12.5%)	**6 (37.5%)**	--	2 (20.0%)	2 (20.0%)	--	**4 (40.0%)**	--	--	--	**--**
Neutropenia	--	--	1 (6.3%)	--	**1 (6.3%)**	--	2 (20.0%)	3 (30.0%)	1 (10.0%)	**6 (60.0%)**	--	--	--	**--**
Lymphocyte Count Decrease	--	--	--	--	**--**	1 (10.0%)	--	1 (10.0%)	1 (10.0%)	**3 (30.0%)**	--	--	--	**--**
Anemia	--	--	1 (6.3%)	--	**1 (6.3%)**	--	1 (10.0%)	1 (10.0%)	--	**2 (20.0%)**	--	--	--	**--**
Other														
Hematuria	--	--	--	--	**--**	2 (20.0%)	--	--	--	**2 (20.0%)**	--	--	--	**--**
Blurred Vision	1 (6.3%)	1 (6.3%)	--	--	**2 (12.5%)**	--	--	--	--	**--**	--	--	--	**--**

Adverse Events ARMs SdB, SdP, SdL: All patients in each arm were evaluable for safety. The adverse event profile for each arm is listed separately. The most common adverse events across all ARMs SdB, SdP, SdL include: anorexia, nausea, fatigue, and thrombocytopenia.

Cohort, Prior Therapies, Time on Study, & Response



Efficacy: ARMs SdB, SdP, SdL

Best Responses* Arms SdB, SdP, SdL as of 8-June-2016									
Treatment Arm	**N**	**ORR (%)**	**CR (%)**	**VGPR (%)**	**PR (%)**	**MR (%)**	**SD (%)**	**PD (%)**	**CBR (%)**
SdB – All Patients[1]	16	**11 (69%)**	1 (6%)	3 (19%)	7 (44%)	3 (19%)	1 (6%)	1 (6%)	**14 (88%)**
SdB – Proteasome Inhibitor Refractory[2]	10	**7 (70%)**	1 (10%)	1 (10%)	5 (50%)	1 (10%)	1 (10%)	1 (10%)	**8 (80%)**
SdP[3,4]	7	**4 (57%)**	--	1 (14%)	3 (43%)	1 (14%)	2 (29%)	--	**5 (71%)**
SdL[5]	1	**1 (100%)**	--	--	1 (100%)	--	--	--	**1 (100%)**

*Responses were adjudicated according to the *International Myeloma Working Group* criteria. ORR=Overall Response Rate (VGPR +PR), CR=Complete Response, 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 8-June-2016 based on interim unaudited data.

[1]Includes 3 patients on treatment with unconfirmed VGPRs, 5 patients on treatment with unconfirmed PRs
[2]Seven out of 10 patients who have responded on the SdB Arm have either bortezomib & carfilzomib-refractory (N=2), bortezomib-refractory (N=7), or carfilzomib-refractory (N=1) MM
[3]Includes 2 patients on treatment with unconfirmed PRs
[4]All responders have lenalidomide-refractory MM
[5]Includes 1 patient on treatment with an unconfirmed PR

Summary and Conclusions

- Dose escalation is still ongoing in all ARMs, SdB, SdP, SdL. No DLTs have been observed
- The most common adverse reactions across all ARMs SdB, SdP, SdL include: anorexia, nausea, fatigue, and thrombocytopenia, mainly grades 1 and 2.
  - Although early, adverse reactions are similar to, or lower than, selinexor or backbone therapy used separately
- Even with dose escalations continuing, responses seen in both selinexor + pomalidomide + dex and selinexor + bortezomib + dex cohorts are encouraging
- In many of the responding patients with heavily pretreated refractory MM, the addition of selinexor seems to restore sensitivity to their previous therapies
- In patients with relapsed/refractory MM whose disease has progressed despite available therapies, these new combinations can help with the urgent need to induce deeper and more durable responses