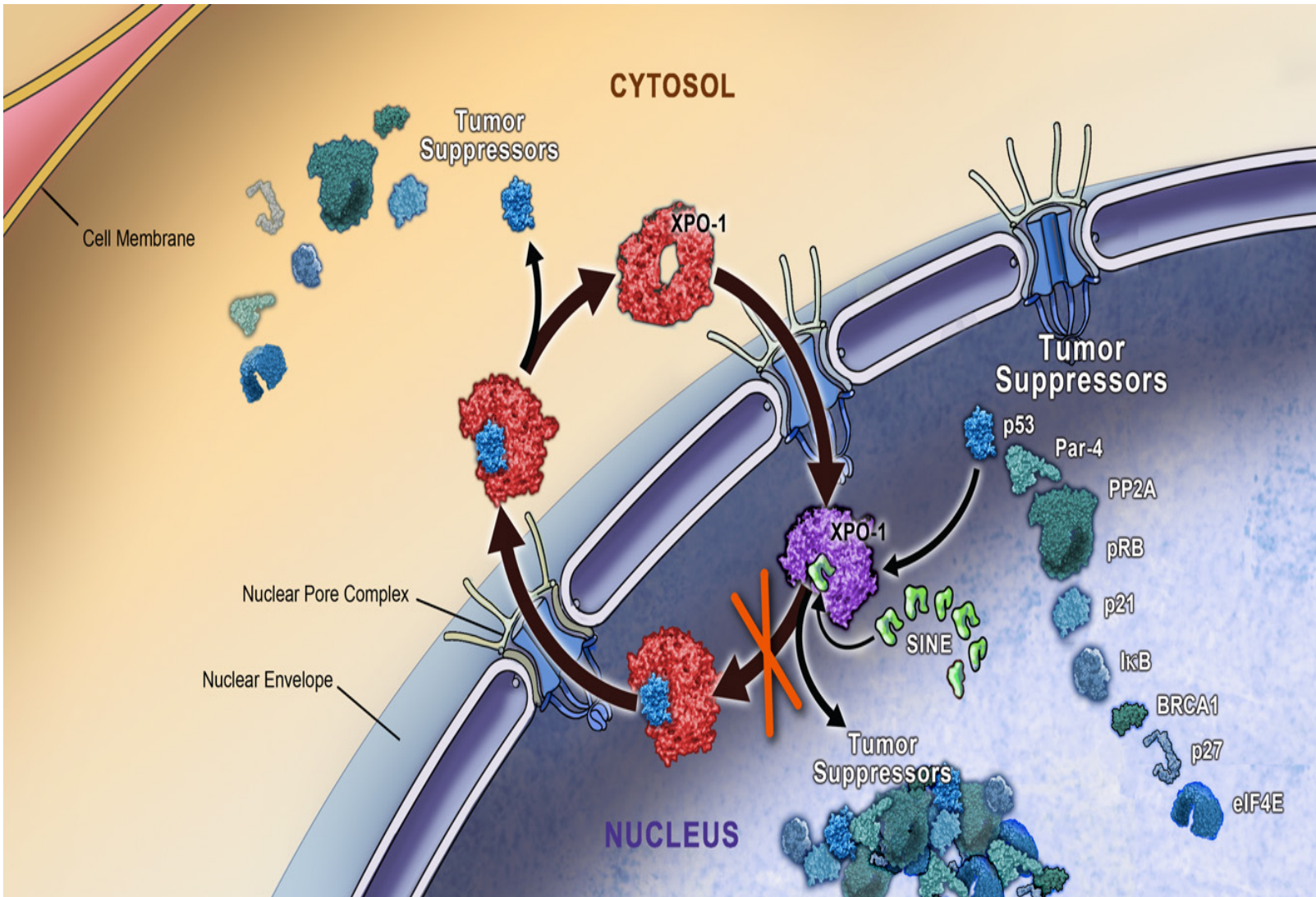


# A Phase 1b Study to Assess the Combination of Selinexor and Daratumumab (SDd) in Patients with Relapsed / Refractory Multiple Myeloma Previously Exposed to Proteasome Inhibitors and Immunomodulatory Drugs

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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 sensitizes multiple myeloma patient cells to daratumumab to induce apoptosis

# 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

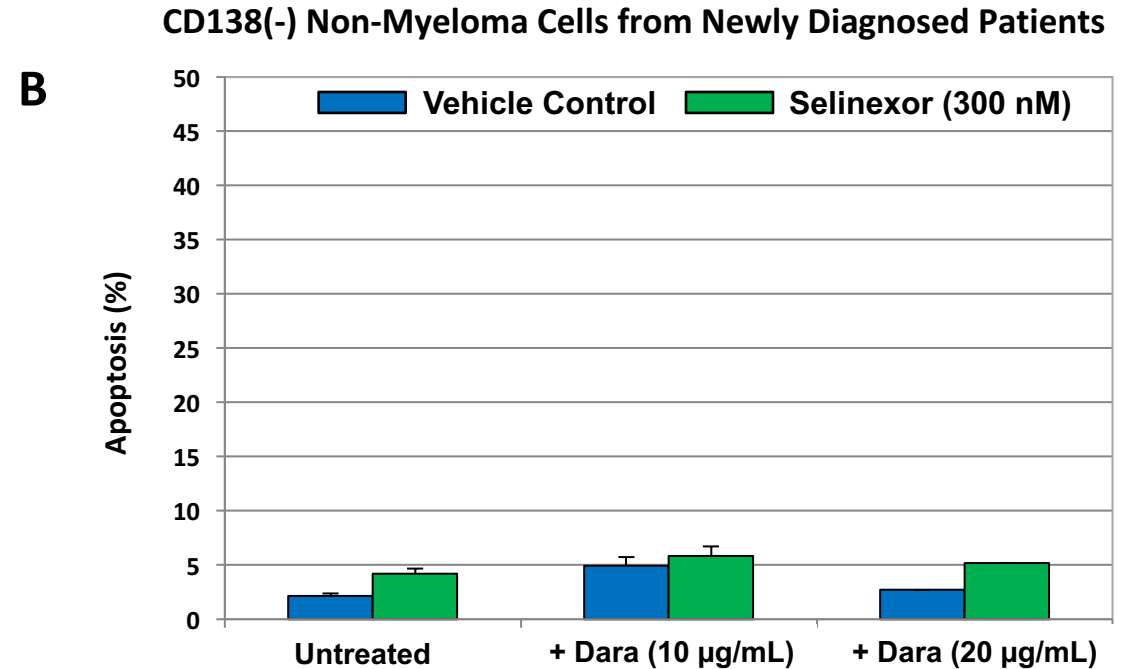
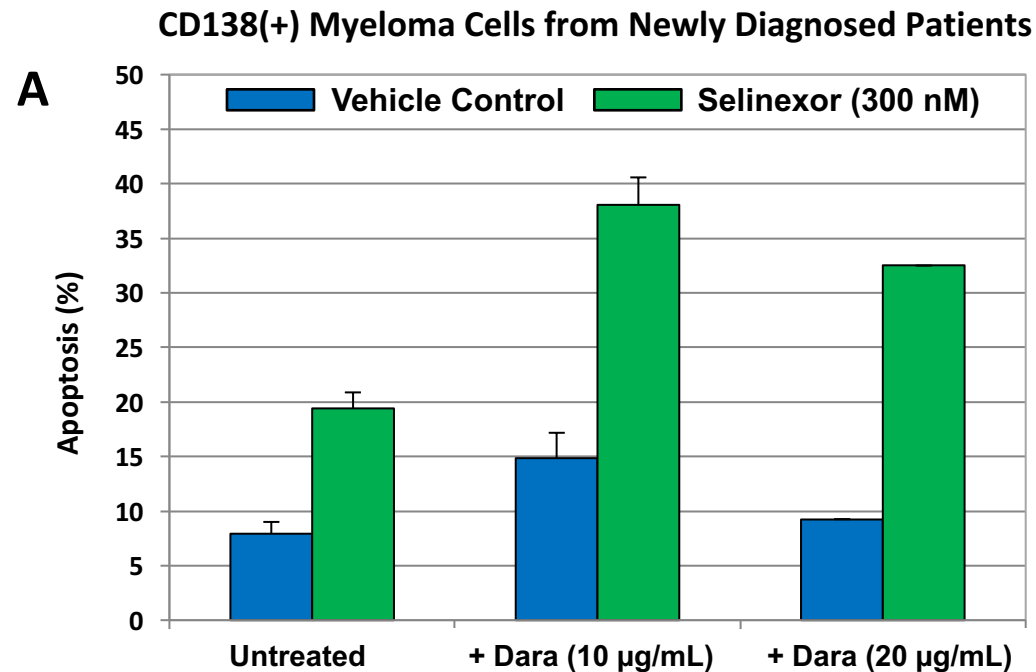
# STOMP Study Design (Cont.)

- **Patient Population SdD:** Patients who received  $\geq 3$  prior lines of therapy, including a PI and an IMiD, or patients with MM refractory to both a PI and an IMiD
- **SdD 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. Daratumumab 16 mg/kg will be evaluated QW. Once the MTD in a cohort is reached, additional patients will be added to determine RP2D.

Drug	SVd ARM	SPd ARM	SRd ARM	SDd ARM
<b>Selinexor, Oral</b>	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
<b>Bortezomib, SC</b>	1.3 mg/m <sup>2</sup> –QW/BIW	--	--	--
<b>Pomalidomide, PO</b>	--	3 – 4 mg, QD	--	--
<b>Lenalidomide, PO</b>	--	--	25 mg, QD	--
<b>Daratumumab, IV</b>	--	--	--	16 mg/kg, QW
<b>Dexamethasone, Oral</b>	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 SDd arm. BIW=Twice Weekly, QW=Once Weekly, Dexamethasone will be dosed on selinexor dosing days

# SDd *Ex-Vivo*: Newly Diagnosed MM Patient Cells



Turner et. al 2017 unpublished

**Selinexor (sel) sensitizes MM cells from newly diagnosed patients to the monoclonal antibody, daratumumab (dara).** Bone marrow mononuclear cells were isolated and treated concurrently with Sel (300 nM) +/- dara 10 or 20 µg/mL for 20 hours. Cells were fluorescently labeled with antibodies against activated caspase 3, CD138, and light chain (kappa or lambda). **(A)** CD138(+) Myeloma Cells (from newly diagnosed MM patients) were sensitized to the combination of Sel (300 nM) / Dara (10 µg) as compared to single agent Sel ( $p=0.005$ ) or Dara ( $p=0.004$ ). **(B)** CD138(-) Non-Myeloma “Normal” Cells (from the same newly diagnosed MM patients) were not sensitized to Sel, Dara, or the combination of Sel (300 nM) / Dara (10 or 20 µg/mL).

# SDd Patient Characteristics

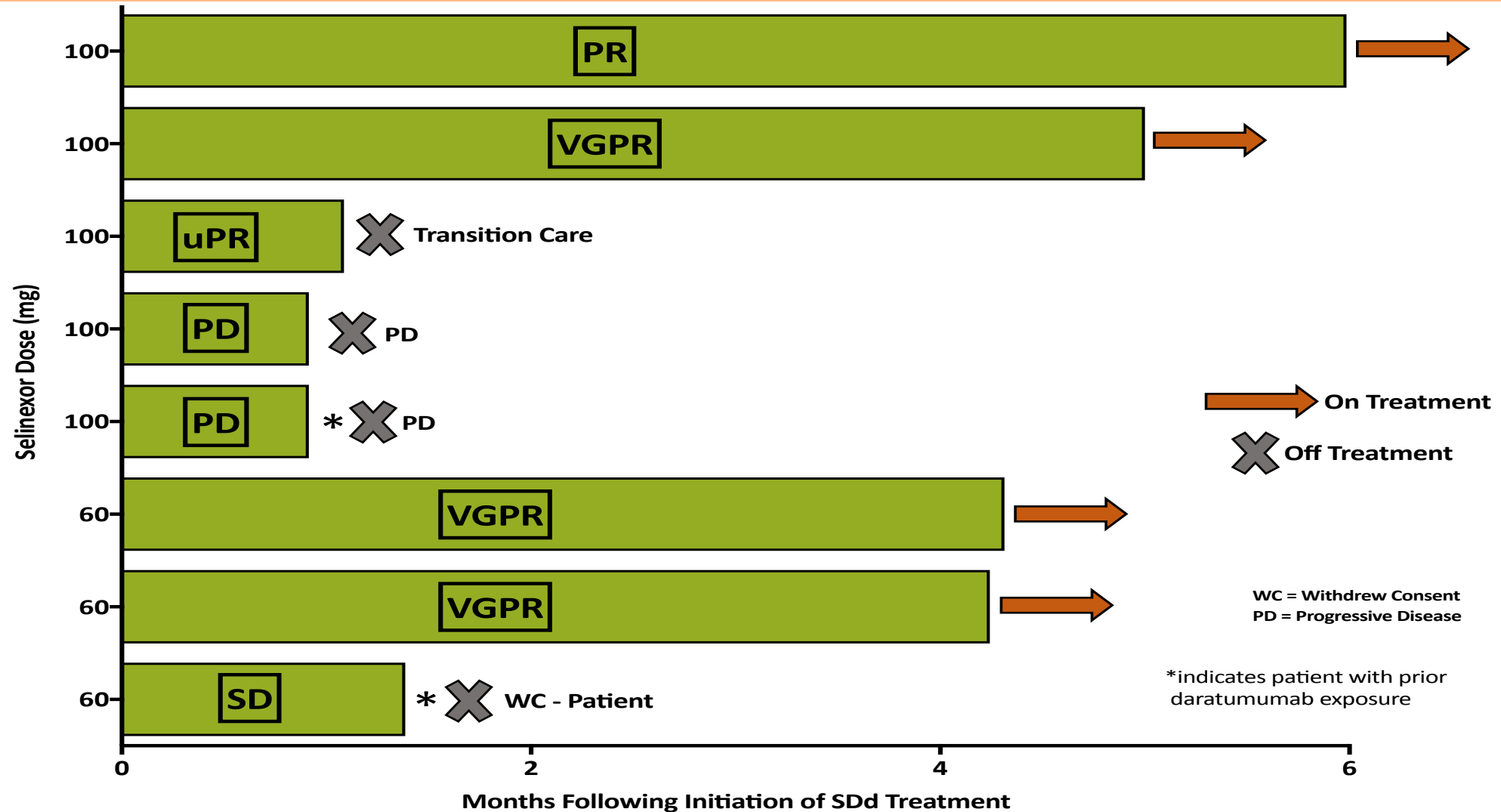
SDd Patient Characteristics	N
<b>Patients Enrolled as of November 1, 2017</b>	<b>9</b>
-60 mg selinexor BIW + 16 mg/kg daratumumab QW	3
<b>-100 mg selinexor QW + 16 mg/kg daratumumab QW (RP2D)</b>	<b>6</b>
Median Age, Years (range)	67 (53 – 74)
Males : Females	7 M : 2 F
Median Years from Diagnosis to SDd Treatment, Years (range)	3 (1 – 12)
<b>Median Prior Regimens (range)</b>	<b>4 (2 – 10)</b>
-Refractory to Prior Proteasome Inhibitor Therapy	9 (100%)
-Refractory to Prior Immunomodulatory Drug Therapy	8 (89%)
-Prior Immunomodulatory Drug + Proteasome Inhibitor Therapy	8 (89%)
-Prior Stem Cell Transplant	8 (89%)
-Prior Daratumumab Therapy	2 (22%)
<b>ISS at Diagnosis</b>	
ISS I	3 (33%)
ISS II	1 (11%)
ISS III	2 (22%)
Unknown	3 (33%)

# SDd Related Adverse Events ≥ 2 Patients

AE Term	60 mg Sel BIW + 16 mg/kg Dara QW (N=3)				100 mg Sel QW + 16 mg/kg Dara QW RP2D (N=6)				Total (N=9)
	Grade 1/2	Grade 3	Grade 4	Total	Grade 1/2	Grade 3	Grade 4	Total	
<b>Gastrointestinal</b>									
Nausea	2 (66.7%)	--	--	<b>2 (66.7%)</b>	1 (16.7%)	--	--	<b>1 (16.7%)</b>	<b>3 (33.3%)</b>
Constipation	2 (66.7%)	--	--	<b>2 (66.7%)</b>	--	--	--	--	<b>2 (22.2%)</b>
Diarrhoea	2 (66.7%)	--	--	<b>2 (66.7%)</b>	--	--	--	--	<b>2 (22.2%)</b>
Vomiting	2 (66.7%)	--	--	<b>2 (66.7%)</b>	--	--	--	--	<b>2 (22.2%)</b>
<b>Constitutional</b>									
Fatigue	3 (100.0%)	--	--	<b>3 (100.0%)</b>	1 (16.7%)	1 (16.7%)	--	<b>2 (33.3%)</b>	<b>5 (55.6%)</b>
<b>Hematologic</b>									
Leukopenia	1 (33.3%)	2 (66.7%)	--	<b>3 (100.0%)</b>	1 (16.7%)	2 (33.3%)	--	<b>3 (50.0%)</b>	<b>6 (66.7%)</b>
Neutropenia	2 (66.7%)	1 (33.3%)	--	<b>3 (100.0%)</b>	1 (16.7%)	2 (33.3%)	--	<b>3 (50.0%)</b>	<b>6 (66.7%)</b>
Thrombocytopenia	--	2 (66.7%)	1 (33.3%)	<b>3 (100.0%)</b>	1 (16.7%)	1 (16.7%)	1 (16.7%)	<b>3 (50.0%)</b>	<b>6 (66.7%)</b>
Anaemia	1 (33.3%)	2 (66.7%)	--	<b>3 (100.0%)</b>	--	2 (33.3%)	--	<b>2 (33.3%)</b>	<b>5 (55.6%)</b>
Lymphopenia	2 (66.7%)	--	--	<b>2 (66.7%)</b>	--	1 (16.7%)	1 (16.7%)	<b>2 (33.3%)</b>	<b>4 (44.4%)</b>
<b>Other</b>									
Alanine Aminotransferase Increased	2 (66.7%)	--	--	<b>2 (66.7%)</b>	--	--	--	--	<b>2 (22.2%)</b>
Aspartate Aminotransferase Increased	2 (66.7%)	--	--	<b>2 (66.7%)</b>	--	--	--	--	<b>2 (22.2%)</b>
Dyspnea	2 (66.7%)	--	--	<b>2 (66.7%)</b>	--	--	--	--	<b>2 (22.2%)</b>
Dizziness	1 (33.3%)	--	--	<b>1 (33.3%)</b>	1 (16.7%)	--	--	<b>1 (16.7%)</b>	<b>2 (22.2%)</b>
Hyperglycemia	--	--	--	--	2 (33.3%)	--	--	<b>2 (33.3%)</b>	<b>2 (22.2%)</b>
Hyponatraemia	--	--	--	--	2 (33.3%)	--	--	<b>2 (33.3%)</b>	<b>2 (22.2%)</b>

**Related Adverse Events SDd Patients:** The most common adverse events include: nausea, fatigue, leukopenia, neutropenia and thrombocytopenia. GI adverse events were generally manageable with antiemetics. MTD was not reached. Two DLT's were reported in the 60 mg BIW cohort: G3 thrombocytopenia and G2 fatigue, both associated with a dose reduction. Based on tolerability and efficacy, the RP2D of SDd is selinexor 100 mg, daratumumab 16 mg/kg and dex 40 mg, all given QW.

# SDd Time on Study & Best Response



Four of nine patients remain on treatment. Responses were rapid in onset with a median time to response 1 month. (One patient not shown: one dose and withdrew consent due to a daratumumab related infusion reaction)



# SDd Efficacy

## Best Responses<sup>†</sup> in Evaluable SDd Patients as of November 15<sup>th</sup>, 2017

Category	N*	ORR (%)	CBR (%)	VGPR (%)	PR <sup>‡</sup> (%)	MR (%)	SD (%)	PD (%)
<b>All</b>	8	<b>5 (63%)</b>	5 (63%)	3 (38%)	2 (25%)	--	1 (13%)	2 (25%)
<b>Daratumumab Naïve</b>	6	<b>5 (83%)</b>	5 (83%)	3 (50%)	2 (33%)	--	--	1 (17%)

<sup>†</sup>Responses were adjudicated according to the *International Myeloma Working Group* criteria,\*one patient not evaluable for response withdrew consent prior to disease follow up. <sup>‡</sup>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 (ORR+MR). Responses as of November 15, 2017 based on interim unaudited data.

# Summary and Conclusions

- **Selinexor can be safely combined with daratumumab and low dose dexamethasone (SDd) in patients with very heavily pretreated MM**
  - **The most common AEs are: nausea, fatigue, leukopenia, neutropenia and thrombocytopenia.**
  - **The combination of SdD is active and the preliminary results of combination of SDd are promising**
    - **ORR of 83% in daratumumab naïve, PI & IMiD refractory MM patients;**
    - **Compares favorably to dara expected ORR <30%**
    - **Responses seen with SDd are rapid and occur within a median of 1 cycle of treatment**
    - **ORR of 63% (all patients including dara refractory)**
- **Additional patients will be enrolled at the RP2D of SDd: selinexor 100 mg, daratumumab 16 mg/kg and dexamethasone 40 mg, all given once-weekly**