A Phase 1b Study using the Combination of Selinexor, Daratumumab, and Dexamethasone in Multiple Myeloma Patients Previously Exposed to Proteasome Inhibitors and Immunomodulatory Drugs

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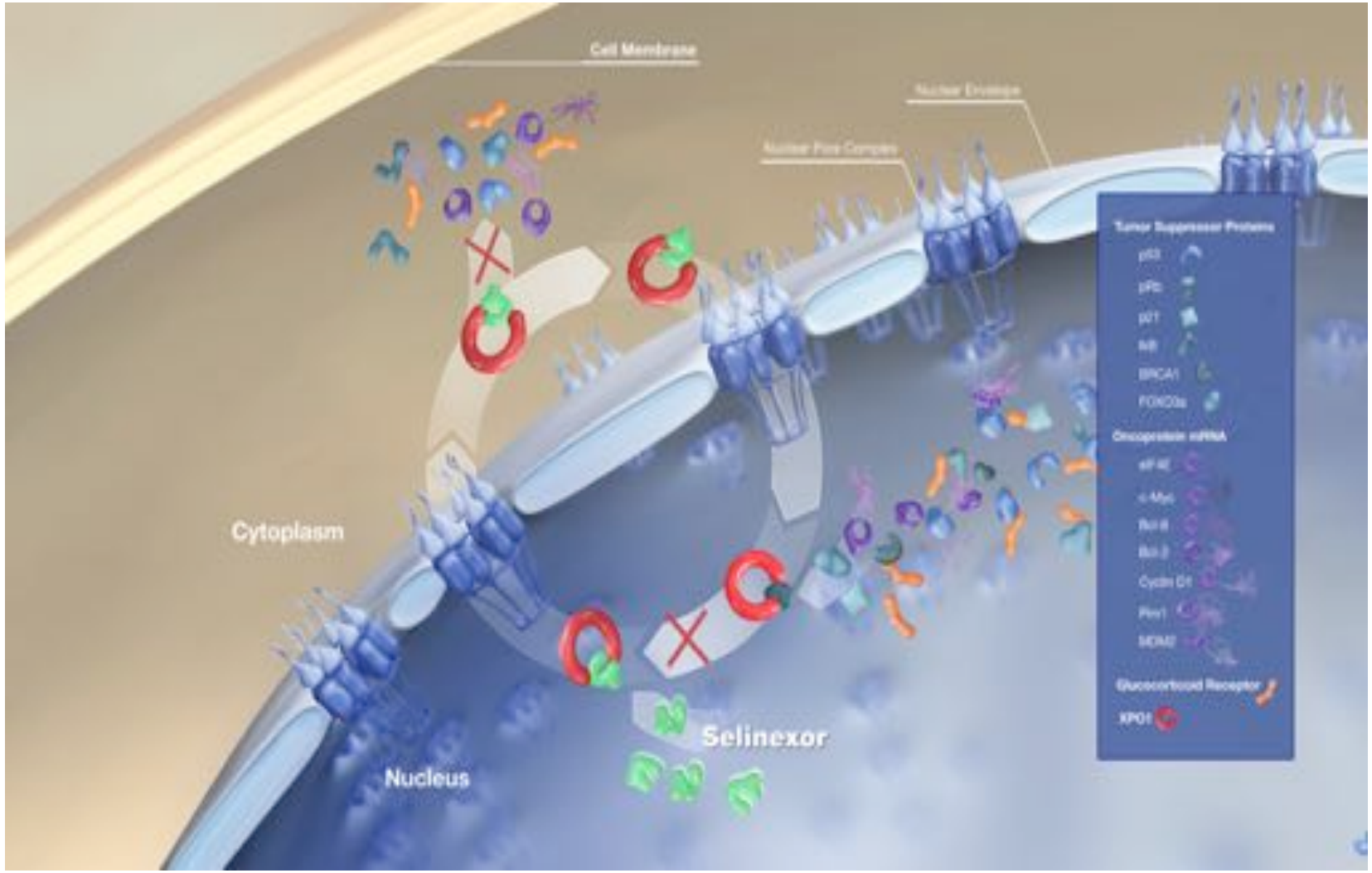
Selinexor Mechanism of Action



- 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 nuclear export (SINE) compound:
  - Reactivates multiple TSPs relevant to MM including p53, IκB and FOXO
  - Reduces c-Myc levels
  - Overcomes MDM2-mediated p53 degradation
- Data suggests selinexor synergizes with daratumumab to induce apoptosis in multiple myeloma patient cells

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) 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

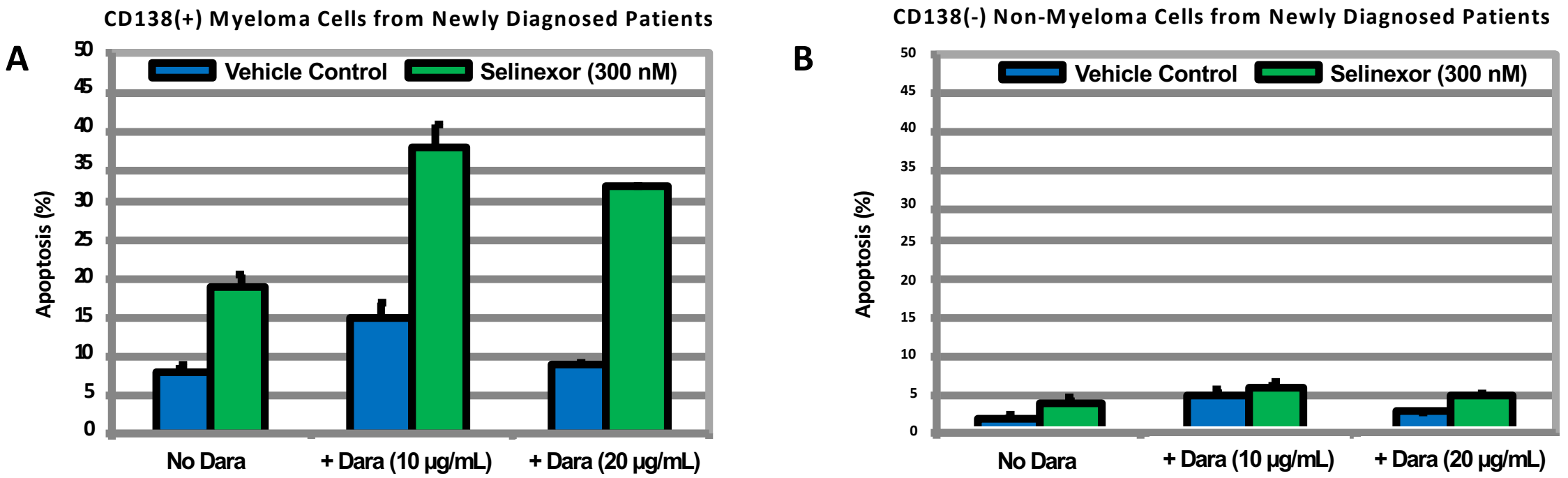
STOMP Study Design (Cont.)

- **Patient Population SDd**: Patients who received ≥ 3 prior lines of therapy for MM, 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 administered per approved dosing. 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	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 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) appears to sensitize 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) had low levels of apoptosis when treated wtih Sel, Dara, or the combination of Sel (300 nM) / Dara (10 or 20 µg/mL).

SDd Patient Characteristics

SDd Patient Characteristics	N
Enrolled as of June 5, 2018	**21**
-60 mg selinexor BIW + 16 mg/kg daratumumab QW	3
-100 mg selinexor QW + 16 mg/kg daratumumab (RP2D)	**18**
Median Age, Years (range)	68 (52 – 77)
Males : Females	9 M : 12 F
Median Years from Diagnosis to SDd Treatment, Years (range)	5 (1 – 12)
Median Prior Regimens (range)	**4 (2 – 10)**
-Proteasome Inhibitor Therapy	21 (100%)
-Immunomodulatory Drug Therapy	21 (100%)
-Stem Cell Transplant	15 (71%)
-Daratumumab Therapy	2 (10%)
International Staging System (ISS) at Diagnosis	
ISS Stage I	7 (33%)
ISS Stage II	1 (5%)
ISS Stage III	4 (19%)
ISS Stage Unknown	9 (43%)

SDd Treatment Related Adverse Events ≥ 3 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=18)				Total (N=21)
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=3)**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=18)**	
Leukopenia	1 (33.3%)	2 (66.7%)	--	**3 (100.0%)**	3 (16.7%)	7 (38.9%)	--	**10 (55.6%)**	**13 (61.9%)**
Thrombocytopenia	--	2 (66.7%)	1 (33.3%)	**3 (100.0%)**	3 (16.7%)	3 (16.7%)	4 (22.2%)	**10 (55.6%)**	**13 (61.9%)**
Neutropenia	2 (66.7%)	1 (33.3%)	--	**3 (100.0%)**	2 (11.1%)	6 (33.3%)	--	**8 (44.4%)**	**11 (52.4%)**
Anemia	1 (33.3%)	2 (66.7%)	--	**3 (100.0%)**	2 (11.1%)	5 (27.8%)	--	**7 (38.9%)**	**10 (47.6%)**
Lymphocytopenia	1 (33.3%)	1 (33.3%)	--	**2 (66.7%)**	1 (5.6%)	3 (16.7%)	1 (5.6%)	**5 (27.8%)**	**7 (33.3%)**
Gastrointestinal									
Nausea	3 (100.0%)	--	--	**3 (100.0%)**	7 (38.9%)	--	--	**7 (38.9%)**	**10 (47.6%)**
Diarrhea	2 (66.7%)	--	--	**2 (66.7%)**	3 (16.7%)	1 (5.6%)	--	**4 (22.2%)**	**6 (28.6%)**
Anorexia	1 (33.3%)	--	--	**1 (33.3%)**	4 (22.2%)	--	--	**4 (22.2%)**	**5 (23.8%)**
Constipation	2 (66.7%)	--	--	**2 (66.7%)**	3 (16.7%)	--	--	**3 (16.7%)**	**5 (23.8%)**
Vomiting	--	--	--	**--**	3 (16.7%)	--	--	**3 (16.7%)**	**3 (14.3%)**
Constitutional									
Fatigue	2 (66.7%)	1 (33.3%)	--	**3 (100.0%)**	6 (33.3%)	1 (5.6%)	--	**7 (38.9%)**	**10 (47.6%)**
Dyspnea	2 (66.7%)	--	--	**2 (66.7%)**	2 (11.1%)	--	--	**2 (11.1%)**	**4 (19.0%)**
Weight Loss	1 (33.3%)	--	--	**1 (33.3%)**	2 (11.1%)	--	--	**2 (11.1%)**	**3 (14.3%)**
Other									
Hyponatremia	--	--	--	**--**	4 (22.2%)	3 (16.7%)	--	**7 (38.9%)**	**7 (33.3%)**
Vision Blurred	--	--	--	**--**	3 (16.7%)	--	--	**3 (16.7%)**	**3 (14.3%)**

- MTD was not reached
- Two DLT's were reported see below
- Based on tolerability and efficacy, the RP2D of SDd is selinexor 100 mg QW, daratumumab 16 mg/kg (per approved dosing) and dex 40 mg QW

SDd Dose Limiting Toxicities (DLTs)

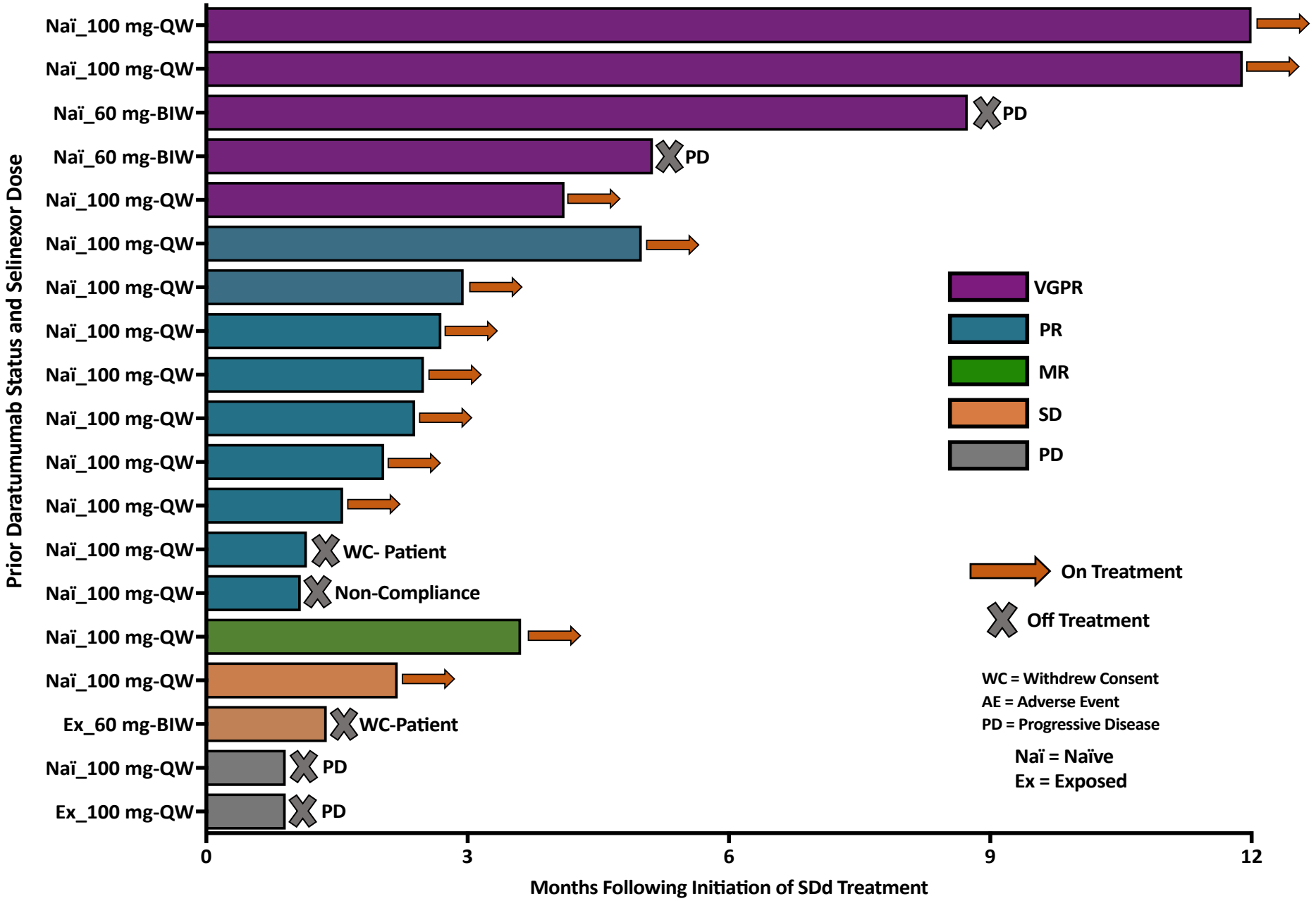
Selinexor Dose	Patients Enrolled	Dose Limiting Toxicities
60 mg BIW	N=3	• Grade 2 Fatigue (requiring dose reduction to 100 mg QW selinexor) • Grade 3 Thrombocytopenia (requiring dose reduction to 100 mg QW selinexor)
100 mg QW	N=6 (5 patients evaluable for DLT)	• No DLT

SDd Efficacy

Best Responses† in Evaluable SDd Patients as of June 5th, 2018								
Category	**N***	**ORR (%)**	**CBR (%)**	**VGPR (%)**	**PR‡ (%)**	**MR (%)**	**SD (%)**	**PD (%)**
Daratumumab Naïve	17	**14 (82%)**	15 (88%)	5 (29%)	9 (53%)	1 (6%)	1 (6%)	1 (6%)
All	19	**14 (74%)**	15 (79%)	5 (26%)	9 (47%)	1 (5%)	2 (11%)	2 (11%)

†Responses were adjudicated according to the *International Myeloma Working Group* criteria,*one patient not evaluable for response withdrew consent prior to disease follow up, one patient pending response. ‡three 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 June 5th, 2018 based on interim unaudited data.

SDd Time on Study & Best Response



Among response evaluable patients: 12 of 19 patients remain on treatment. Responses were rapid in onset with a median time to response of 1 month. *(One patient on treatment not shown: pending response assessment)*

Summary and Conclusions

- Data suggest that selinexor can be safely combined with daratumumab and low dose dexamethasone (SDd) in patients with very heavily pretreated MM
- The most common AEs are: leukopenia neutropenia and thrombocytopenia and low grade nausea and fatigue
- SDd appears active and the preliminary results are promising
  - ORR of 82% in daratumumab naïve, PI & IMiD-refractory or exposed patients with MM
  - ORR of 74% (all patients including dara exposed)
  - Responses seen with SDd occur within a median of 1 cycle of treatment
- Additional patients will be enrolled at the RP2D of SDd: selinexor 100 mg QW, daratumumab 16 mg/kg (per approved dosing) and dexamethasone 40 mg QW