Selinexor Combined with Low Dose Bortezomib and Dexamethasone (SVd) Induces a High Response Rate in Patients with Relapsed or Refractory Multiple Myeloma (MM)

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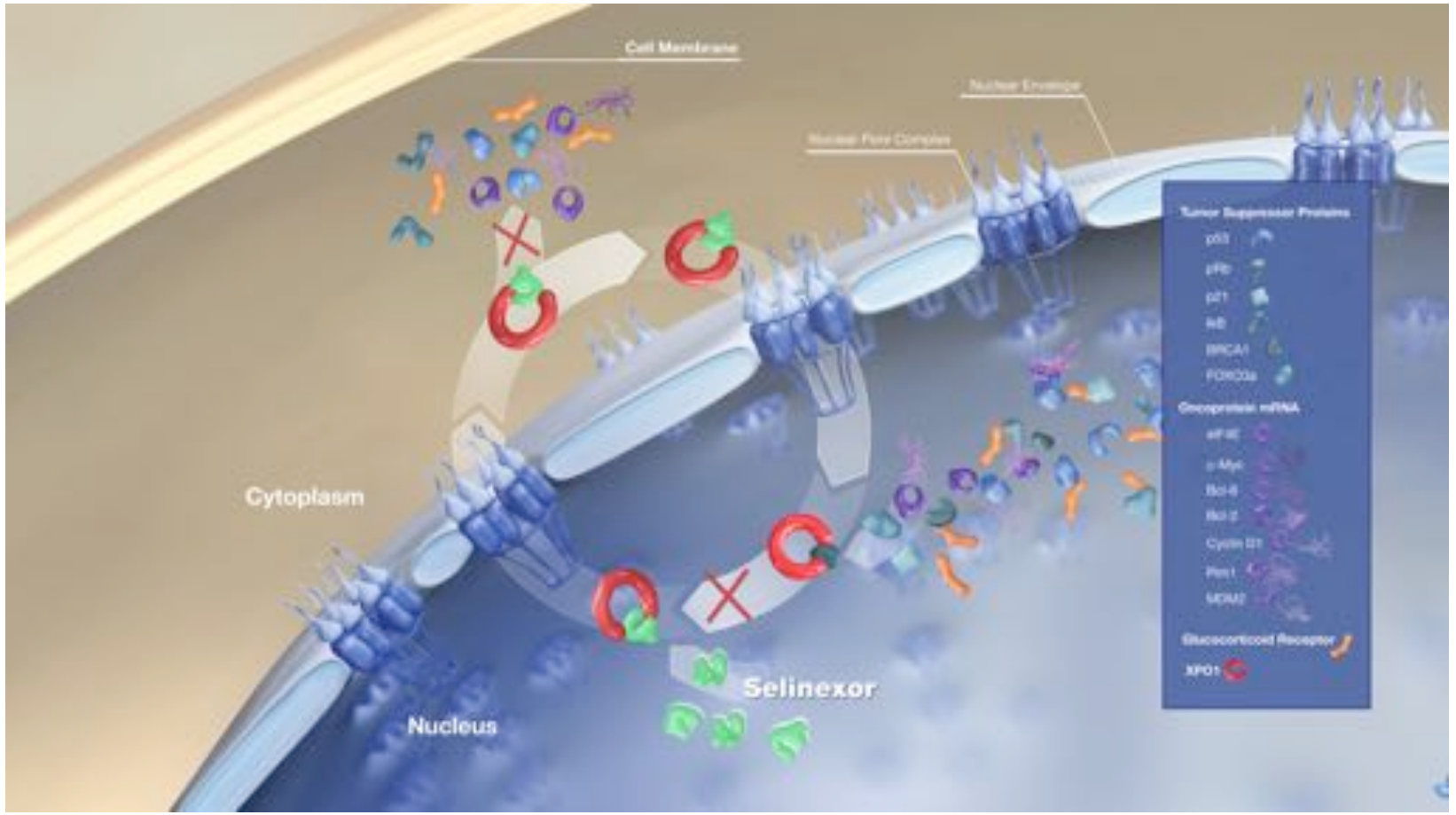
Selinexor Mechanism of Action



- 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

- Selinexor synergizes with proteasome inhibitors (e.g., bortezomib) through:
  - Enhancing levels (by PI) and nuclear retention (by XPO1 inhibition) of multiple TSPs
  - Increasing nuclear IκB levels resulting in inhibition of NFκB transcriptional activity
  - Inducing ribosomal stress response (combination of both PI and XPO1 inhibition)

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 SVd**: Patients whose MM has relapsed after ≥ 1 prior therapy – may include prior bortezomib (V), but not refractory to V in their most recent line of therapy
- **SVd 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. V dosing will be evaluated QW vs. BIW. 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 SVd arm. BIW=Twice Weekly, QW=Once Weekly, Dexamethasone will be dosed on selinexor dosing days

SVd Patient Characteristics

SVd Patient Characteristics	N
Enrolled as of June 5, 2018	42
-60 mg selinexor BIW + 1.3 mg/m^2 bortezomib QW	3
-80 mg selinexor BIW + 1.3 mg/m^2 bortezomib QW	6
-80 mg selinexor QW + 1.3 mg/m^2 bortezomib QW	4
-80 mg selinexor QW + 1.3 mg/m^2 bortezomib BIW	3
-100 mg selinexor QW + 1.3 mg/m^2 bortezomib QW (RP2D)	**26**
Median Age, Years (range)	64 (43 – 75)
Males : Females	23 M : 19 F
Median Years from Diagnosis to SVd Treatment, Years (range)	5 (1 – 19)
Median Prior Regimens (range)	**3 (1 – 11)**
-Proteasome Inhibitor Therapy	38 (90%)
-Refractory to Proteasome Inhibitor Therapy	21 (50%)
-Immunomodulatory Drug Therapy	38 (90%)
-Stem Cell Transplant	31 (74%)
International Staging System (ISS) at Diagnosis	
ISS Stage I	16 (38%)
ISS Stage II	11 (26%)
ISS Stage III	11 (26%)
ISS Stage Unknown	4 (10%)

SVd Treatment Related Adverse Events ≥10% of Patients

AE Term	60/80 mg Sel QW/BIW + 1.3 mg/m^2 Bort QW/BIW (N=16)				100 mg Sel QW + 1.3 mg/m^2 Bort QW RP2D Patients (N=26)				Total (N=42)
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=16)**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=26)**	
Thrombocytopenia	1 (6.3%)	4 (25.0%)	7 (43.8%)	**12 (75.0%)**	1 (3.8%)	3 (11.5%)	5 (19.2%)	**9 (34.6%)**	**21 (50.0%)**
Neutropenia	--	4 (25.0%)	1 (6.3%)	**5 (31.3%)**	1 (3.8%)	6 (23.1%)	--	**7 (26.9%)**	**12 (28.6%)**
Anemia	1 (6.3%)	4 (25.0%)	--	**5 (31.3%)**	3 (11.5%)	1 (3.8%)	--	**4 (15.4%)**	**9 (21.4%)**
Gastrointestinal									
Nausea	5 (31.3%)	2 (12.5%)	--	**7 (43.8%)**	20 (76.9%)	--	--	**20 (76.9%)**	**27 (64.3%)**
Anorexia	8 (50.0%)	1 (6.3%)	--	**9 (56.3%)**	16 (61.5%)	--	--	**16 (61.5%)**	**25 (59.5%)**
Diarrhea	7 (43.8%)	2 (12.5%)	--	**9 (56.3%)**	10 (38.5%)	1 (3.8%)	--	**11 (42.3%)**	**20 (47.6%)**
Vomiting	4 (25.0%)	1 (6.3%)	--	**5 (31.3%)**	8 (30.8%)	--	--	**8 (30.8%)**	**13 (31.0%)**
Altered Taste	2 (12.5%)	--	--	**2 (12.5%)**	4 (15.4%)	--	--	**4 (15.4%)**	**6 (14.3%)**
Constitutional									
Fatigue	9 (56.3%)	--	--	**9 (56.3%)**	10 (38.5%)	6 (23.1%)	--	**16 (61.5%)**	**25 (59.5%)**
Weight loss	5 (31.3%)	--	--	**5 (31.3%)**	5 (19.2%)	--	--	**5 (19.2%)**	**10 (23.8%)**
Dehydration	2 (12.5%)	--	--	**2 (12.5%)**	3 (11.5%)	--	--	**3 (11.5%)**	**5 (11.9%)**
Other									
Vision Blurred	2 (12.5%)	--	--	**2 (12.5%)**	6 (23.1%)	--	--	**6 (23.1%)**	**8 (19.0%)**
Edema	4 (25.0%)	--	--	**4 (25.0%)**	3 (11.5%)	--	--	**3 (11.5%)**	**7 (16.7%)**
Peripheral Neuropathy	2 (12.5%)	--	--	**2 (12.5%)**	4 (15.4%)	--	--	**4 (15.4%)**	**6 (14.3%)**
Cataract	3 (18.8%)	--	1 (6.3%)	**4 (25.0%)**	2 (7.7%)	--	--	**2 (7.7%)**	**6 (14.3%)**
Confusion	1 (6.3%)	1 (6.3%)	--	**2 (12.5%)**	3 (11.5%)	--	--	**3 (11.5%)**	**5 (11.9%)**
Hyponatremia	2 (12.5%)	--	--	**2 (12.5%)**	1 (3.8%)	2 (7.7%)	--	**3 (11.5%)**	**5 (11.9%)**

Treatment Related Adverse Events as of June 5th, 2018

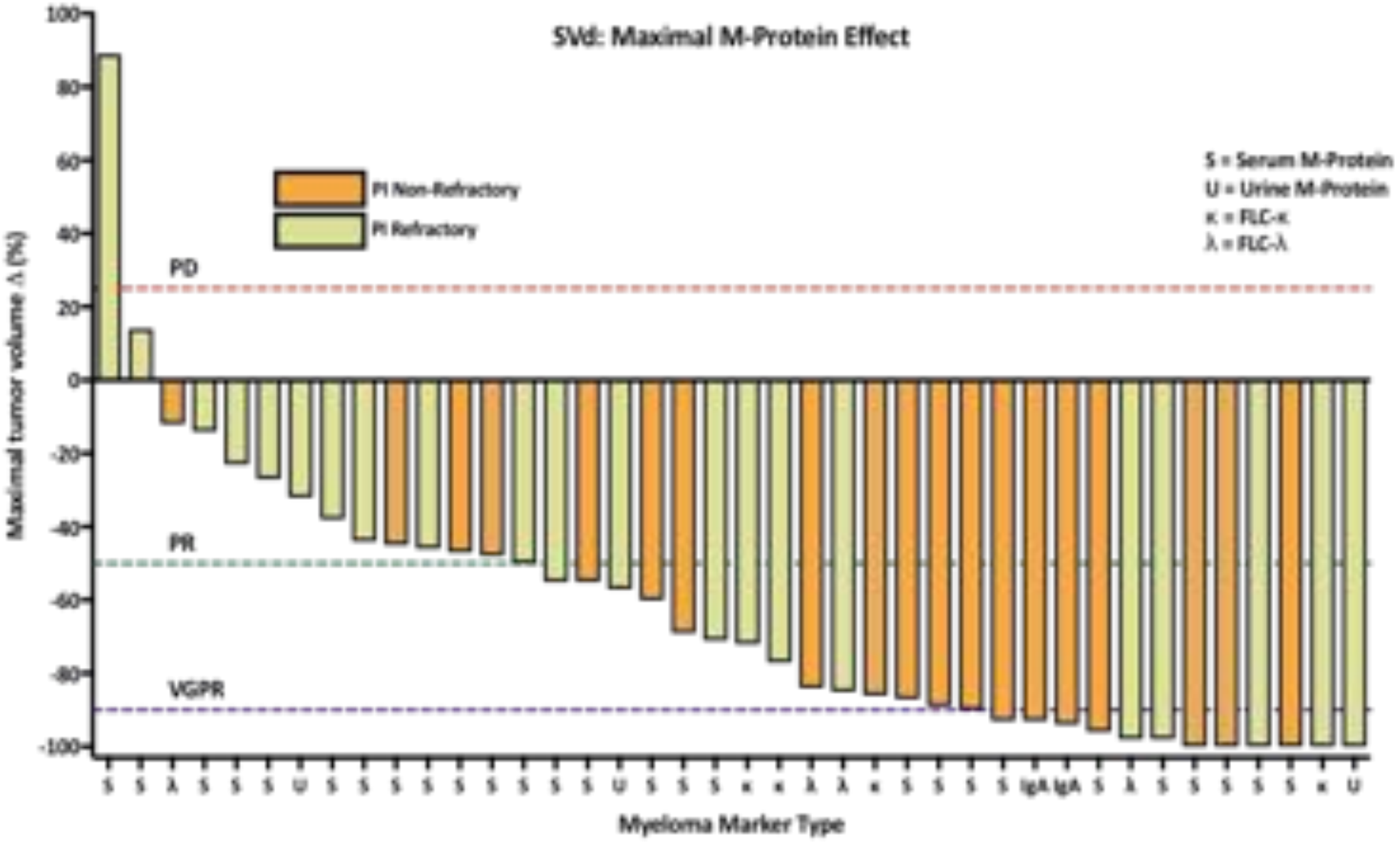
- MTD was not reached. No DLT's were reported.
- All three patients in the BIW bortezomib (V) cohort were reduced to QW V after Cycle 1 for tolerability issues.
- Peripheral neuropathy (all cases unrelated to Sel) was limited to 6 patients (14.3%) (G1: 4 patients, G2: 2 patients) of which 5 had prior V exposure.
- Based on tolerability and efficacy, the RP2D of SVd is Sel 100 mg, V 1.3 mg/m^2 and dex 40 mg, all QW (40% less V and 25% less dex compared to the standard, approved BIW schedule of Vd).

SVd Efficacy

Best Responses† in Evaluable SVd Patients as of June 5th, 2018										
Category	**N***	**ORR (%)**	**CBR (%)**	**sCR (%)**	**CR (%)**	**VGPR (%)**	**PR‡ (%)**	**MR (%)**	**SD (%)**	**PD (%)**
PI Relapsed or Naïve	19	**16 (84%)**	**18 (95%)**	1 (5%)	3 (16%)	3 (16%)	9 (47%)	2 (11%)	1 (5%)	--
PI Refractory	21	**9 (43%)**	**14 (67%)**	--	1 (5%)	4 (19%)	4 (19%)	5 (24%)	6 (29%)	1 (5%)
PI Relapsed or Naïve, ≤ 3 Prior Treatments (BOSTON)**	18	**15 (83%)**	**16 (89%)**	1 (6%)	3 (17%)	4 (22%)	7 (39%)	1 (6%)	2 (11%)	--

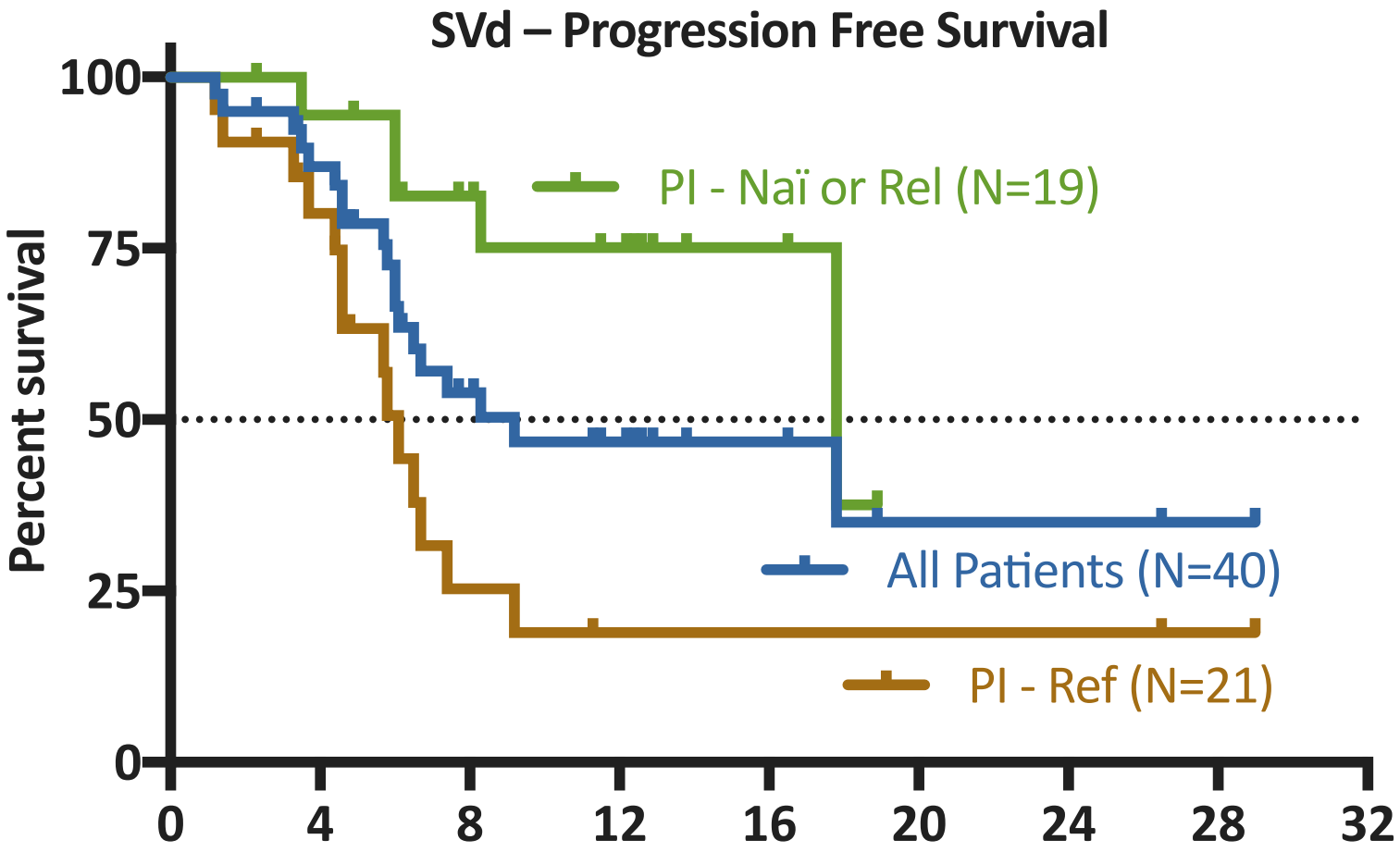
†Responses were adjudicated according to the *International Myeloma Working Group* criteria, **two patients not evaluable for response: one death unrelated to myeloma and one withdrawal of consent before disease follow up.* ‡one unconfirmed PR. ORR=Overall Response Rate (sCR+CR+VGPR+PR), sCR=Stringent Complete Response, CR=Complete Response, 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. **BOSTON: patient population eligible for the ongoing Phase 3 Randomized BOSTON Study of SVd versus Vd.

SVd PFS, M-Protein Effect, Time on Study & Response



A) Thirty eight of 40 patients evaluable for response had reductions in M-protein; 27 patients (68%) had M-protein reductions of at least 50% including 13 patients (33%) with M-protein reductions ≥90%.

SVd PFS, M-Protein Effect, Time on Study & Response

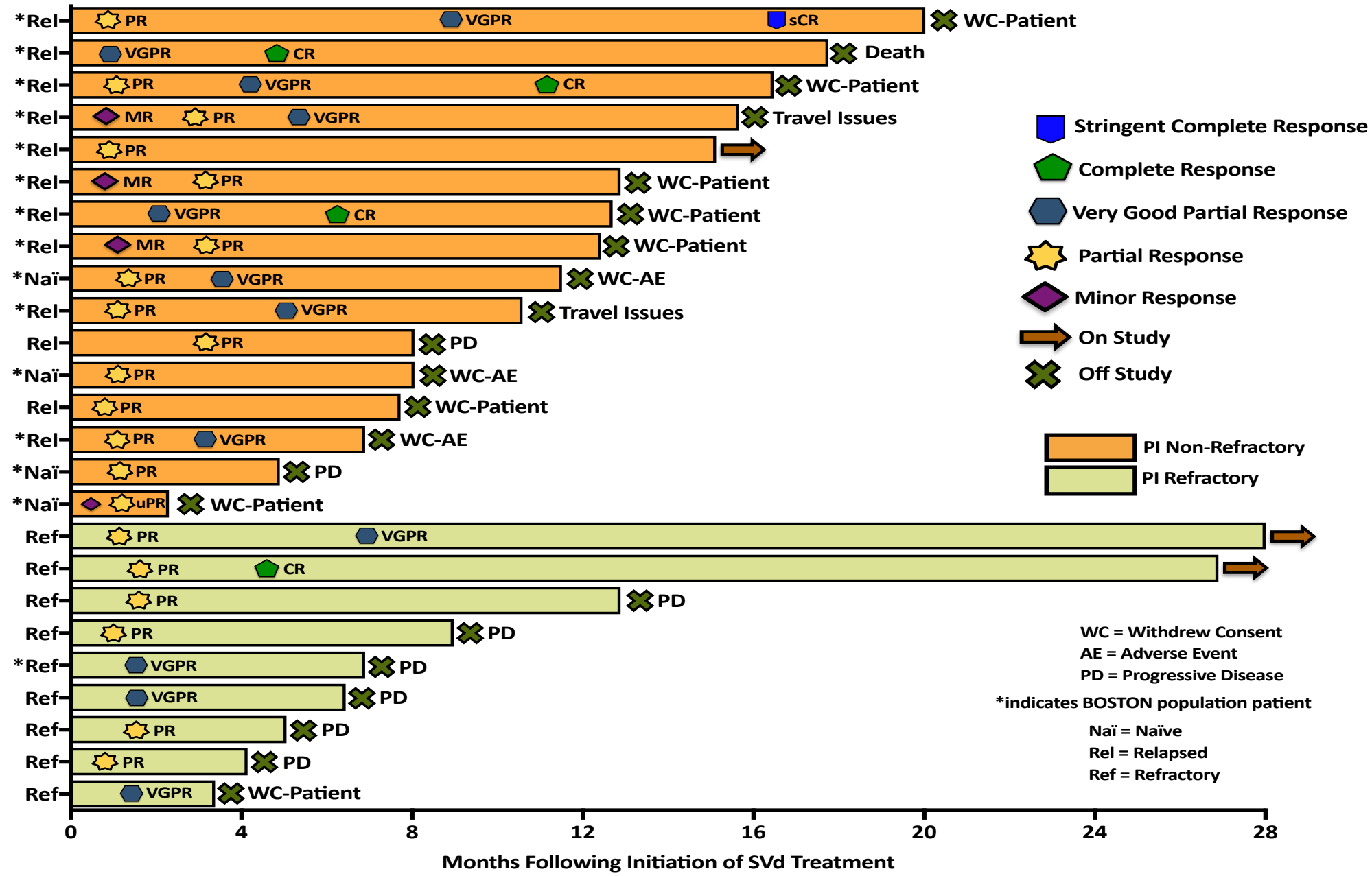


Patients at Risk

Months	0	3.7	4.9	6.1	8.3	12.2	13.8	16.5	18.9	26.5	29
All Patients	40	33	27	22	15	11	6	5	3	2	1
PI Naï or Rel	19	18	17	16	11	9	4	3	1	--	--
PI Ref	21	16	11	8	5	3	--	--	--	2	1

C) Median PFS among all evaluable patients is 9.2 months with a median follow up of 12.4 months. PI naïve or relapsed MM 17.8 months (same for BOSTON population patients 17.8 months, N=18). Patients with PI refractory MM was 6.1 months.

SVd PFS, M-Protein Effect, Time on Study & Response



B) Among responders (N=25) the median time on treatment was 10.5 months. Responses were rapid in onset with a median time to response of 1.1 months. The median duration of response is ~13 months (BOSTON patients DOR also ~13 months).

Summary and Conclusions

- Data suggests that selinexor can be safely combined with bortezomib (V) and low dose dexamethasone (SVd) in patients with heavily pretreated MM
  - Most common AEs: anorexia, nausea, fatigue (mainly grades 1-2), and thrombocytopenia (minimal bleeding)
  - Peripheral neuropathy, a major AE in treatment with V, was limited to 6 patients (14.3%) on SVd treatment
- ORR of 84% in patients with PI relapsed or naïve MM; compares with Vd alone expected ORR ≤ 65%
  - ORR of 43% in patients with PI refractory MM, supporting preclinical findings that selinexor re-sensitizes and overcomes resistance to PIs
  - ORR of 83% in PI relapsed or naïve patients with ≤ 3 prior treatments, i.e., the "BOSTON" Phase 3 population
  - Responses on SVd are rapid and typically occur within 1 cycle of treatment, often improving over time
  - The PFS is 17.8 months in patients with PI naïve or relapsed MM
- The ORR with SVd is achieved with 40% less V and 25% less dex versus standard Vd, without any overt major organ toxicities
- RP2D of SVd is selinexor 100 mg, V 1.3 mg/m^2 and dexamethasone 40 mg, once-weekly (35 day cycle)
- The high ORR rate and PFS of 17.8 months in patients with ≤ 3 prior therapies treated with SVd support the ongoing Phase 3 BOSTON study examining SVd vs Vd