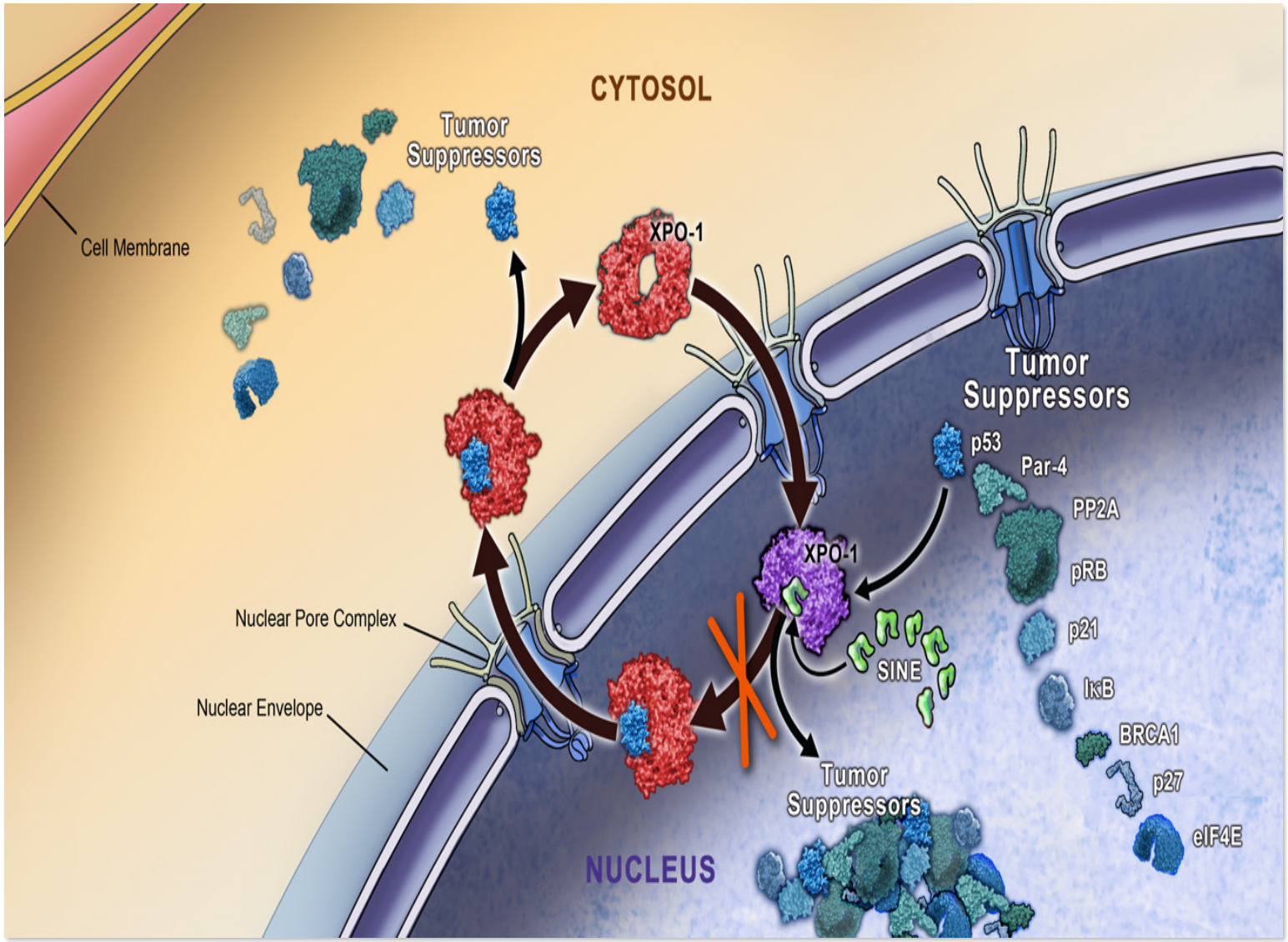
Selinexor in Combination with Weekly Low-Dose Bortezomib and Dexamethasone (SVd) Induces a High Response Rate with Durable Responses in Patients with Refractory Multiple Myeloma

Nizar J. Bahlis[1], Heather Sutherland[2], Darrell White[3], Michael Sebag[4], Suzanne Lentzsch[5], Rami Kotb[6], Chris Venner[7], Cristina Gasparetto[8], Gary Schiller[9], Richard LeBlanc[10], William Bensinger[11], Brea Lipe[12], Aldo Del Col[13], Michael Kauffman[14], Sharon Shacham[14], Jacqueline Jeha[14], Jean-Richard Saint-Martin[14], Jatin Shah[14], Christine Chen[15]

(1) Southern Alberta Cancer Research Institute, Calgary, Alberta (2) Vancouver General Hospital, Vancouver, British Columbia (3) Dalhousie University and QEII Health Sciences Center, Halifax; Nova Scotia (4) Royal Victoria Hospital, Montreal, Québec (5) Columbia University, New York; NY (6) Cancer Care Manitoba, Winnipeg, Manitoba (7) Cross Cancer Institute, Edmonton, Alberta (8) Duke University Cancer Center, Durham, North Carolina (9) David Geffen School of Medicine at UCLA, Los Angeles, California (10) Hôpital Maisonneuve-Rosemont, Montreal, Quebec (11) Swedish Cancer Center, Seattle; WA (12) University of Rochester Medical College, New York, NY (13) Myeloma Canada, Laval, Quebec (14) Karyopharm Therapeutics, Newton, MA (15) Princess Margaret Cancer Center, Toronto, Ontario

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 synergizes with proteasome inhibitors (e.g., bortezomib) through:
  - Enhanced level and nuclear retention of multiple TSPs
  - Increased nuclear IκB retention and inhibition of NFκB transcriptional activity
  - Induction of ribosomal stress response

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 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 ≥ 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
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
Bortezomib, SC	1.3 mg/m^2 –QW/BIW	--	--	--
Pomalidomide, PO	--	3 – 4 mg, QD	--	--
Lenalidomide, PO	--	--	25 mg, QD	--
Daratumumab, IV	--	--	--	16 mg/kg, 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

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
Patients Enrolled as of November 15, 2017	**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)**
-Prior Proteasome Inhibitor Therapy	38 (90%)
-Refractory to Prior Proteasome Inhibitor Therapy	21 (50%)
-Prior Immunomodulatory Drug Therapy	38 (90%)
-Prior Stem Cell Transplant	30 (71%)
ISS at Diagnosis	
ISS I	15 (36%)
ISS II	9 (21%)
ISS III	11 (26%)
Unknown	7 (17%)

SVd 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)
Gastrointestinal	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total**	
Nausea	5 (31.3%)	2 (12.5%)	--	**7 (43.8%)**	19 (73.1%)	--	--	**19 (73.1%)**	**26 (61.9%)**
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%)**	8 (30.8%)	1 (3.8%)	--	**9 (34.6%)**	**18 (42.9%)**
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%)**	3 (11.5%)	--	--	**3 (11.5%)**	**8 (19.0%)**
Dehydration	2 (12.5%)	--	--	**2 (12.5%)**	3 (11.5%)	--	--	**3 (11.5%)**	**5 (11.9%)**
Hematologic									
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%)	5 (19.2%)	--	**6 (23.1%)**	**11 (26.2%)**
Anemia	1 (6.3%)	4 (25.0%)	--	**5 (31.3%)**	2 (7.7%)	1 (3.8%)	--	**3 (11.5%)**	**8 (19.0%)**
Other									
Vision Blurred	2 (12.5%)	--	--	**2 (12.5%)**	6 (23.1%)	--	--	**6 (23.1%)**	**8 (19.0%)**
Peripheral Neuropathy	2 (12.5%)	--	--	**2 (12.5%)**	4 (15.4%)	--	--	**4 (15.4%)**	**6 (14.3%)**
Cataract	3 (18.8%)	--	--	**3 (18.8%)**	2 (7.7%)	--	--	**2 (7.7%)**	**5 (11.9%)**
Confusion	1 (6.3%)	1 (6.3%)	--	**2 (12.5%)**	3 (11.5%)	--	--	**3 (11.5%)**	**5 (11.9%)**
Peripheral Edema	3 (18.8%)	--	--	**3 (18.8%)**	2 (7.7%)	--	--	**2 (7.7%)**	**5 (11.9%)**
Hyponatremia	1 (6.3%)	1 (6.3%)	--	**2 (12.5%)**	1 (3.8%)	1 (3.8%)	--	**2 (7.7%)**	**4 (9.5%)**

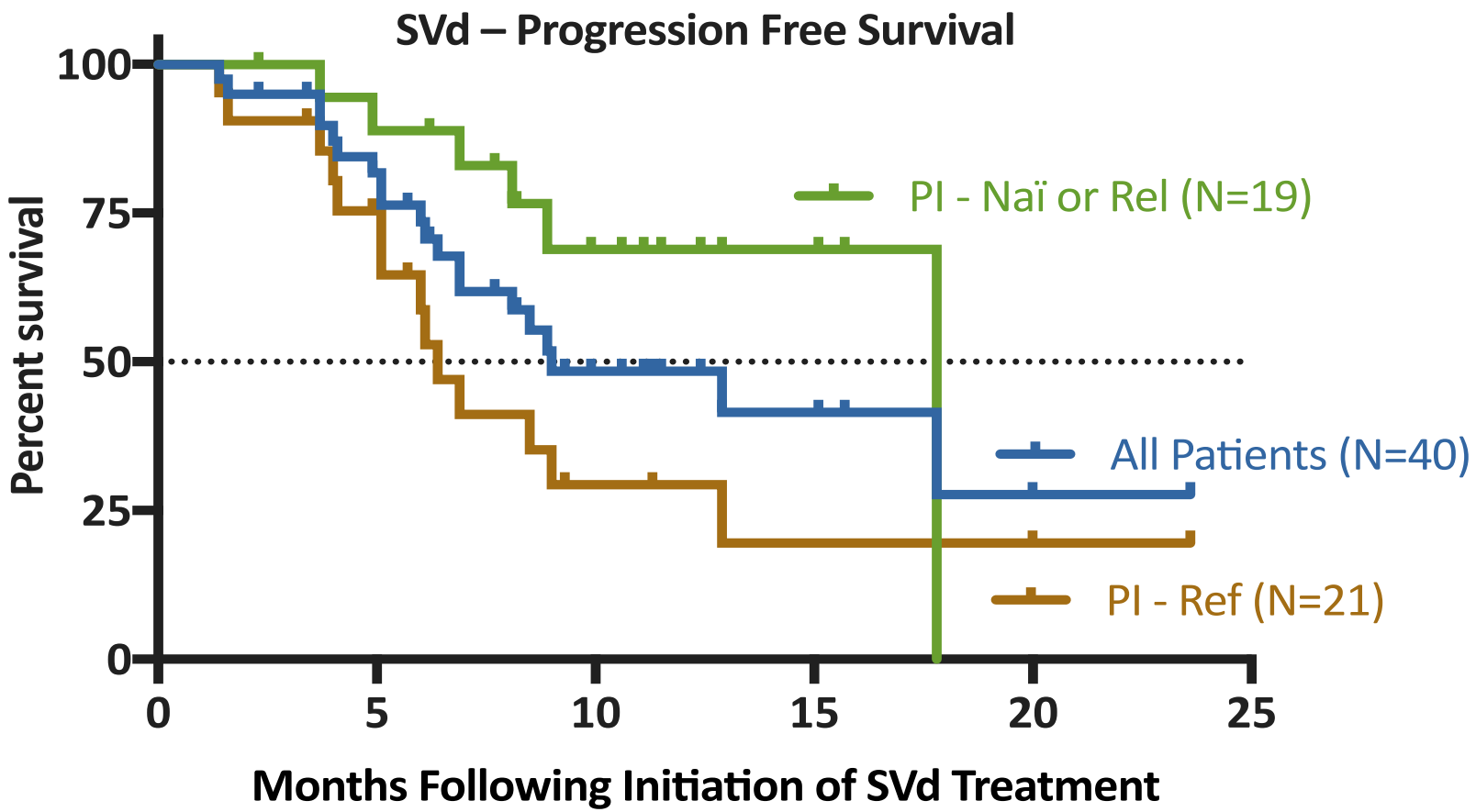
Related Adverse Events SVd Patients: The most common adverse events include: nausea, anorexia, fatigue, (mainly G1/2) and thrombocytopenia (mainly G3/4). GI adverse events were generally manageable with antiemetics. MTD was not reached. No DLT's were reported. All three patients in the BIW bortezomib (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 November 15th, 2017									
Category	**N***	**ORR (%)**	**CBR (%)**	**CR (%)**	**VGPR (%)**	**PR‡ (%)**	**MR (%)**	**SD (%)**	**PD (%)**
PI Relapsed or Naïve	19	**16 (84%)**	**16 (95%)**	2 (11%)	5 (26%)	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%)**	2 (11%)	6 (33%)	7 (39%)	1 (6%)	2 (11%)	--

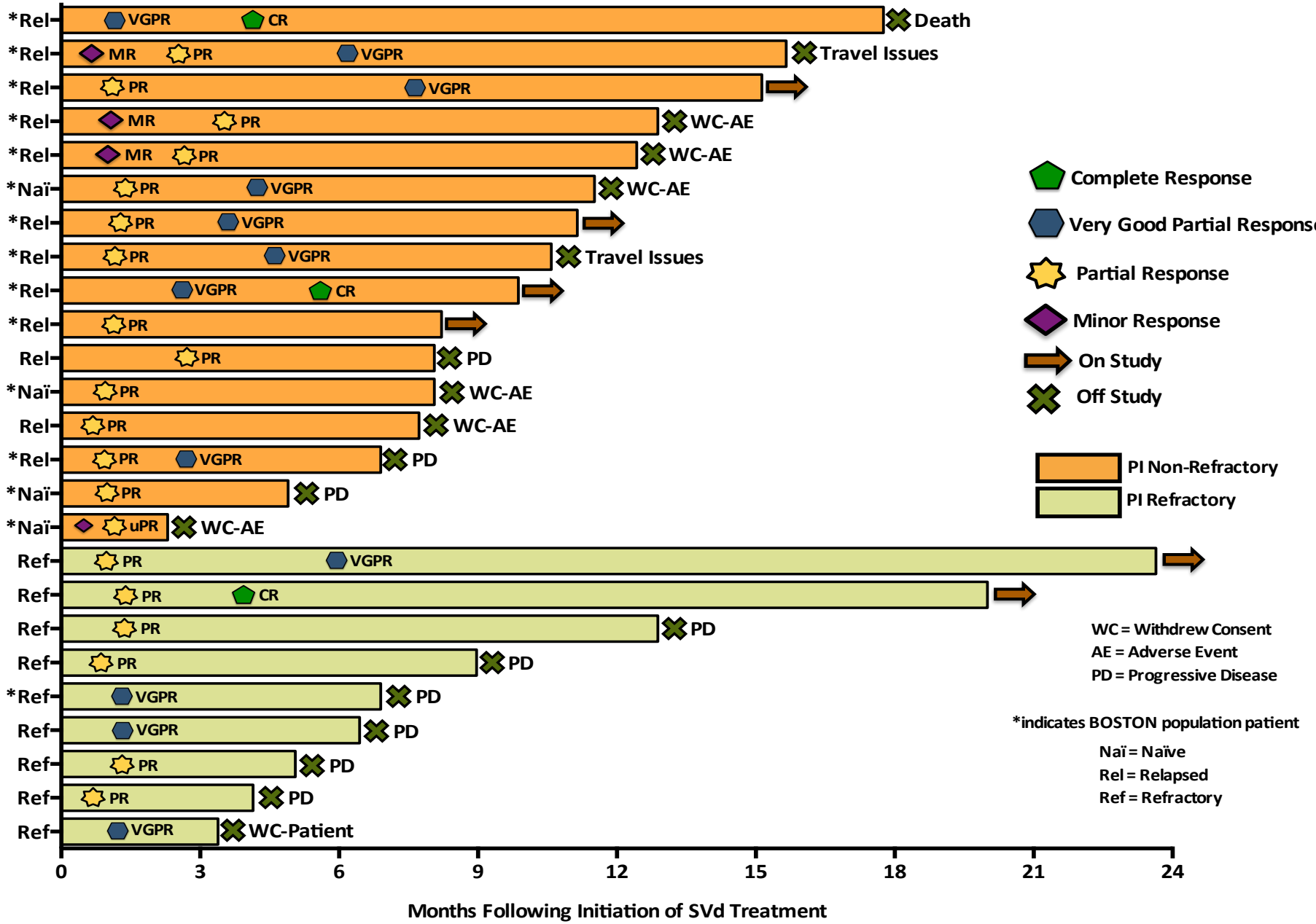
†Responses were adjudicated according to the *International Myeloma Working Group* criteria, **two patients not evaluable for response: one death unrelated to myeloma and one withdrawal of consent before disease follow up.* ‡one unconfirmed PR. ORR=Overall Response Rate (CR+VGPR+PR), CR=Complete Response, VGPR=Very Good Partial Response, PR=Partial Response, MR=Minor Response, SD=Stable Disease, PD=Progressive Disease, CBR=Clinical Benefit Rate (ORR+MR). Responses as of November 15, 2017 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



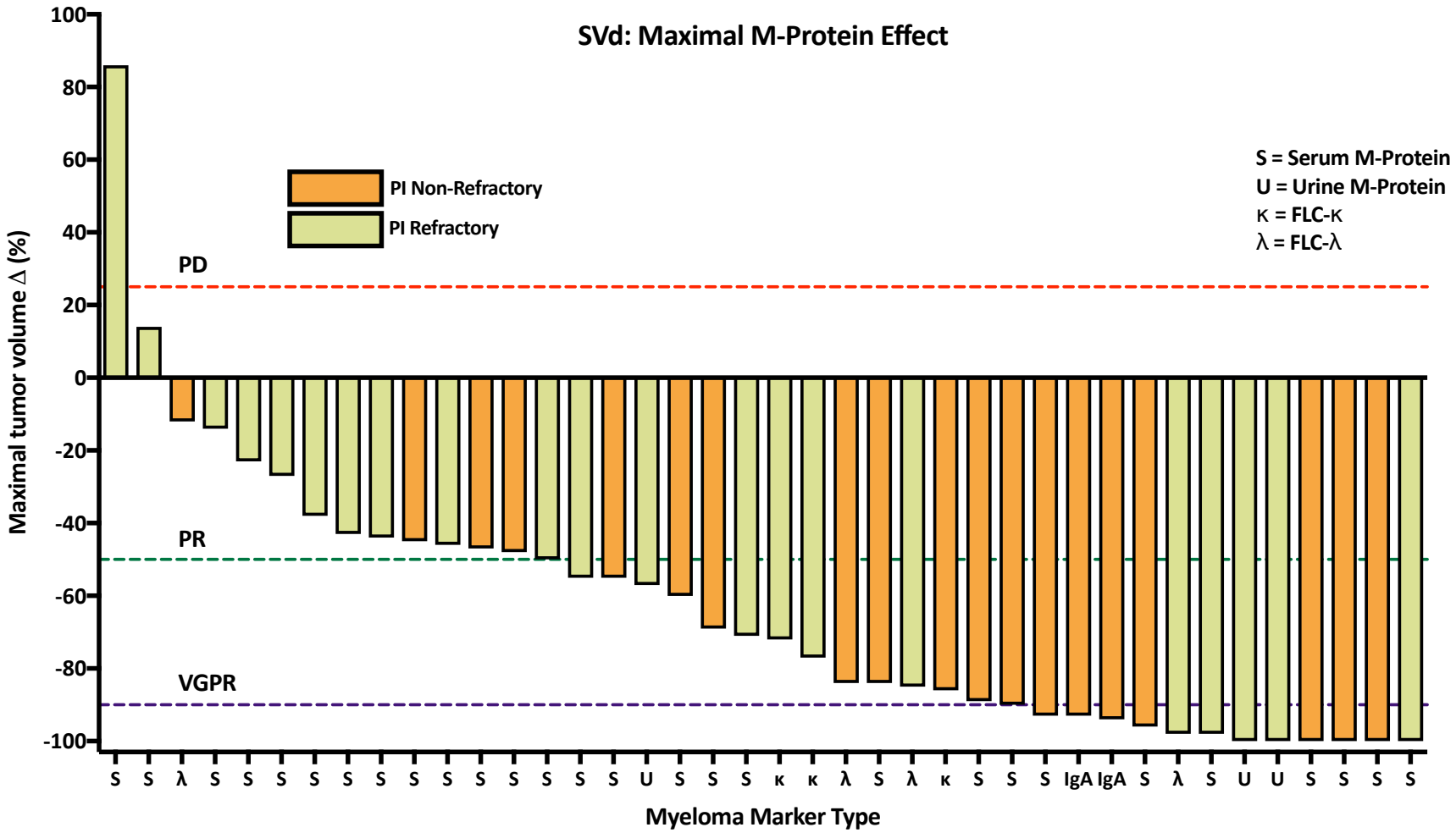
A) Median PFS among all evaluable patients is 9 months with a median follow up of 11.3 months. PI naïve or relapsed MM >13 months (same for BOSTON population patients >13 months, N=18). Patients with PI refractory MM was 6.4 months.

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



B) Among responders (N=25) the median time on treatment was 8.9 months. Responses were rapid in onset with a median time to response of 1.1 months. The median duration of response is ~12 months (BOSTON patients DOR also ~12 months).

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



C) 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%.

Summary and Conclusions

- 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 mainly grades 3/4
  - Peripheral neuropathy, a major AE in treatment with V, was limited to 6 patients (14.3%) on SVd treatment
- The combination of SVd is active and durable with rapid time to response
  - 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 > 13 months in patients with PI naïve or relapsed MM
- The high ORR with SVd is achieved with 40% less V and 25% less dex, without any overt major organ toxicities
- RP2D of SVd is selinexor 100 mg, V 1.3 mg/m^2 and dexamethasone 40 mg, all given once-weekly (35 day cycle)
- The high ORR rate and PFS >13 months in patients with ≤3 prior therapies treated with SVd support the ongoing Phase 3 BOSTON study examining SVd vs Vd