Selinexor in Combination with Bortezomib and Dexamethasone (SVd) Demonstrates Significant Activity in Patients with Refractory MM: Results of Phase I STOMP Trial (MCRN02)

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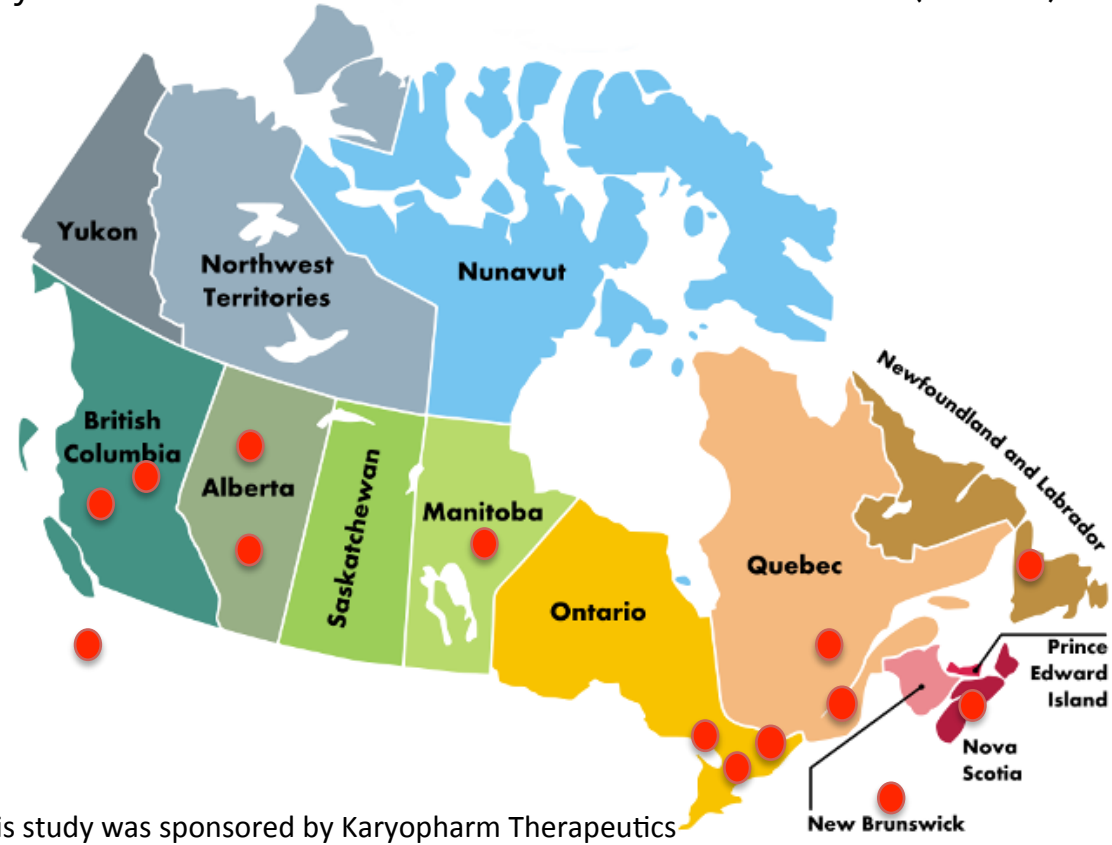

- Southern Alberta Cancer Research Institute
- Cancer Care Manitoba
- Royal Victoria Hospital
- Vancouver General Hospital
- Hôpital Maisonneuve-Rosemont
- Queen Elizabeth II Health Sciences Center
- Cross Cancer Institute
- Juravinski Cancer Centre
- Memorial Hospital of Newfoundland
- The Ottawa Hospital
- Hotel-Dieu de Québec
- Swedish Cancer Center
- Columbia University
- Princess Margaret Cancer Center

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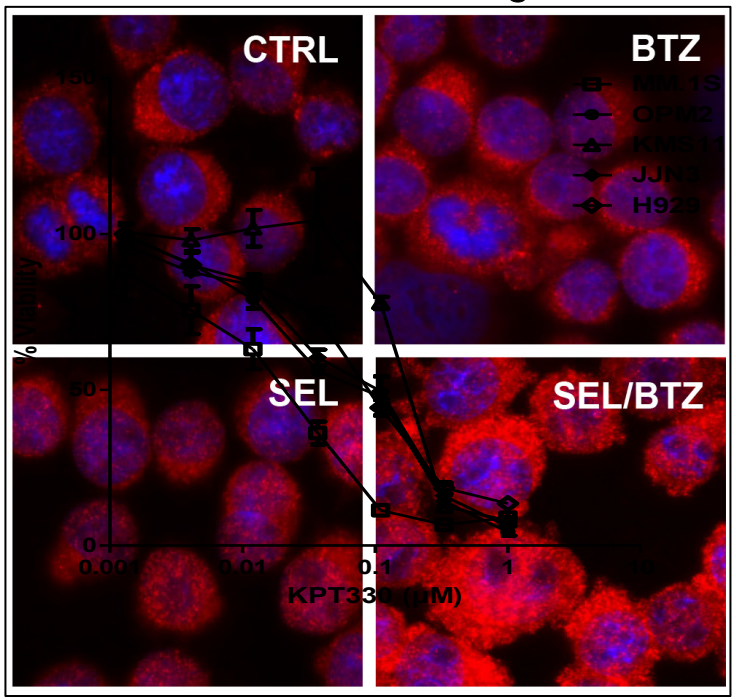
Mechanism of Action – Selinexor + Bortezomib

- Selinexor is a first-in-class exportin 1 (XPO1) inhibitor:
  - Nuclear retention and activation of TSPs
  - Nuclear retention of GR in the presence of steroids
  - Suppresses oncoproteins expression

- Bortezomib is a first-in-class proteasome inhibitor (PI) that inhibits the 26S proteasome disrupting proteins homeostasis and inducing ER stress response.

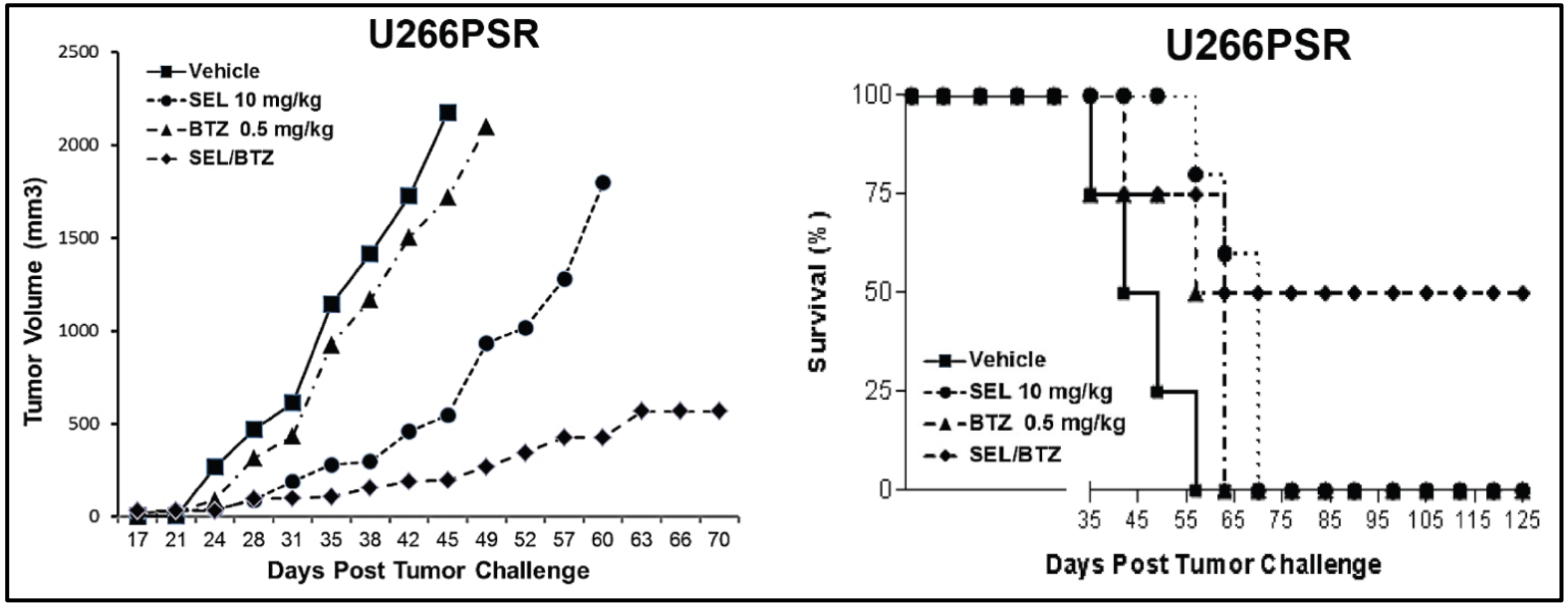
- Selinexor synergizes with PI (bortezomib) through
  - increased nuclear IκB retention and inhibition of NFκB transcriptional activity.
  - Induction of ribosomal stress response.

Selinexor + Bortezomib promotes NFκB-IκBα binding



Selinexor + bortezomib significantly increases nuclear NFκB-IκBα *vs.* selinexor or bortezomib. (*Turner 2016, Oncotarget*)

Preclinical Activity: Selinexor + Bortezomib

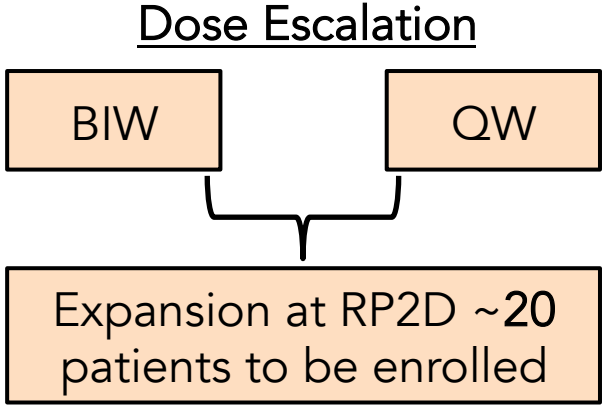


- Selinexor in combination with bortezomib significantly reduced MM tumor growth in the PI-resistant U226PSR tumor xenograft (*Turner 2016, Oncotarget*)

Selinexor and backbone **T**reatments **O**f multiple **M**yeloma **P**atients: **STOMP** Study Design

- <u>Primary Objective</u>: Determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D)
- Patient Populations:
  - Arm SVd: selinexor + bortezomib + dexamethasone
    - MM patients relapsing after ≥ 1 prior therapy may include prior bortezomib, as long as not refractory to bortezomib in their most recent line of therapy
  - Arm SPd: selinexor + pomalidomide + dexamethasone *(ASH 2016 - Poster 3330)*
  - Arm SLd: selinexor + lenalidomide + dexamethasone
- **Dosing Scheme SVd:** A standard 3 + 3 design will be used for dose escalations:

Drug	Selinexor Once Weekly (QW)	Selinexor Twice Weekly (BIW)
Selinexor, oral	Dose Level 1: 80 mg Dose Level 2: 100 mg	Dose Level 1: 60 mg Dose Level 2: 80 mg
Bortezomib, SC	1.3 mg/m^2 QW/BIW	1.3 mg/m^2 QW
Dexamethasone, oral	40 mg QW	20 mg BIW



STOMP – SVd Patient Characteristics

SVd Patient Characteristics	N
Patients Enrolled as of November 1, 2016	33
Escalation Patients : Expansion Patients	22 : 11
Median Age, Years (range)	63 (43 – 74)
Males : Females	19 M : 14 F
High Risk Cytogenetics (del17p, t(4;14), t(14;16))	9 (27%)
Median Prior Regimens (range)	**4 (1 – 11)**
-Prior Proteasome Inhibitor	30 (91%)
-Refractory to Prior Proteasome Inhibitor	24 (73%)
-Refractory to Prior IMiD (Lenalidomide or Pomalidomide)	30 (91%)
-Refractory to Prior Lenalidomide and Pomalidomide	13 (39%)

Treatment Related Adverse Events ≥ 10%

AE Term	60/80 mg Sel BIW + 1.3 mg/m^2 Bort QW N=9				80 mg Sel QW + 1.3 mg/m^2 Bort QW N=4				80 mg Sel QW + 1.3 mg/m^2 Bort BIW N=3				100 mg Sel QW + 1.3 mg/m^2 Bort QW N=6			
Gastrointestinal	Grade 1/2	Grade 3	Grade 4	Total	Grade 1/2	Grade 3	Grade 4	Total	Grade 1/2	Grade 3	Grade 4	Total	Grade 1/2	Grade 3	Grade 4	Total
Anorexia	56%	11%	--	**67%**	25%	--	--	**25%**	33%	--	--	**33%**	33%	--	--	**33%**
Diarrhea	11%	22%	--	**33%**	25%	--	--	**25%**	100%	--	--	**100%**	--	17%	--	**17%**
Nausea	22%	11%	--	**33%**	25%	--	--	**25%**	67%	--	--	**67%**	67%	--	--	**67%**
Vomiting	11%	11%	--	**22%**	25%	--	--	**25%**	33%	--	--	**33%**	33%	--	--	**33%**
Altered Taste	11%	--	--	**11%**	--	--	--	**--**	--	--	--	**--**	17%	--	--	**17%**
Constitutional																
Weight Loss	44%	--	--	**44%**	--	--	--	**--**	--	--	--	**--**	--	--	--	**--**
Fatigue	56%	--	--	**56%**	25%	--	--	**25%**	67%	--	--	**67%**	50%	17%	--	**67%**
Dehydration	--	--	--	**--**	25%	--	--	**25%**	33%	--	--	**33%**	--	--	--	**--**
Hematologic																
Thrombocytopenia	--	33%	33%	**67%**	25%	25%	25%	**75%**	--	--	67%	**67%**	--	17%	--	**17%**
Neutropenia	--	33%	--	**33%**	--	--	--	**--**	--	33%	33%	**67%**	--	--	--	**--**
Anemia	--	33%	--	**33%**	--	--	--	**--**	33%	33%	--	**67%**	17%	--	--	**17%**
Other																
Cognitive Disorder	--	22%	--	**22%**	--	--	--	**--**	--	--	--	**--**	--	--	--	**--**
Epistaxis	11%	--	--	**11%**	--	--	--	**--**	33%	--	--	**33%**	--	--	--	**--**
Vision blurred	11%	--	--	**11%**	--	--	--	**--**	--	--	--	**--**	17%	--	--	**17%**

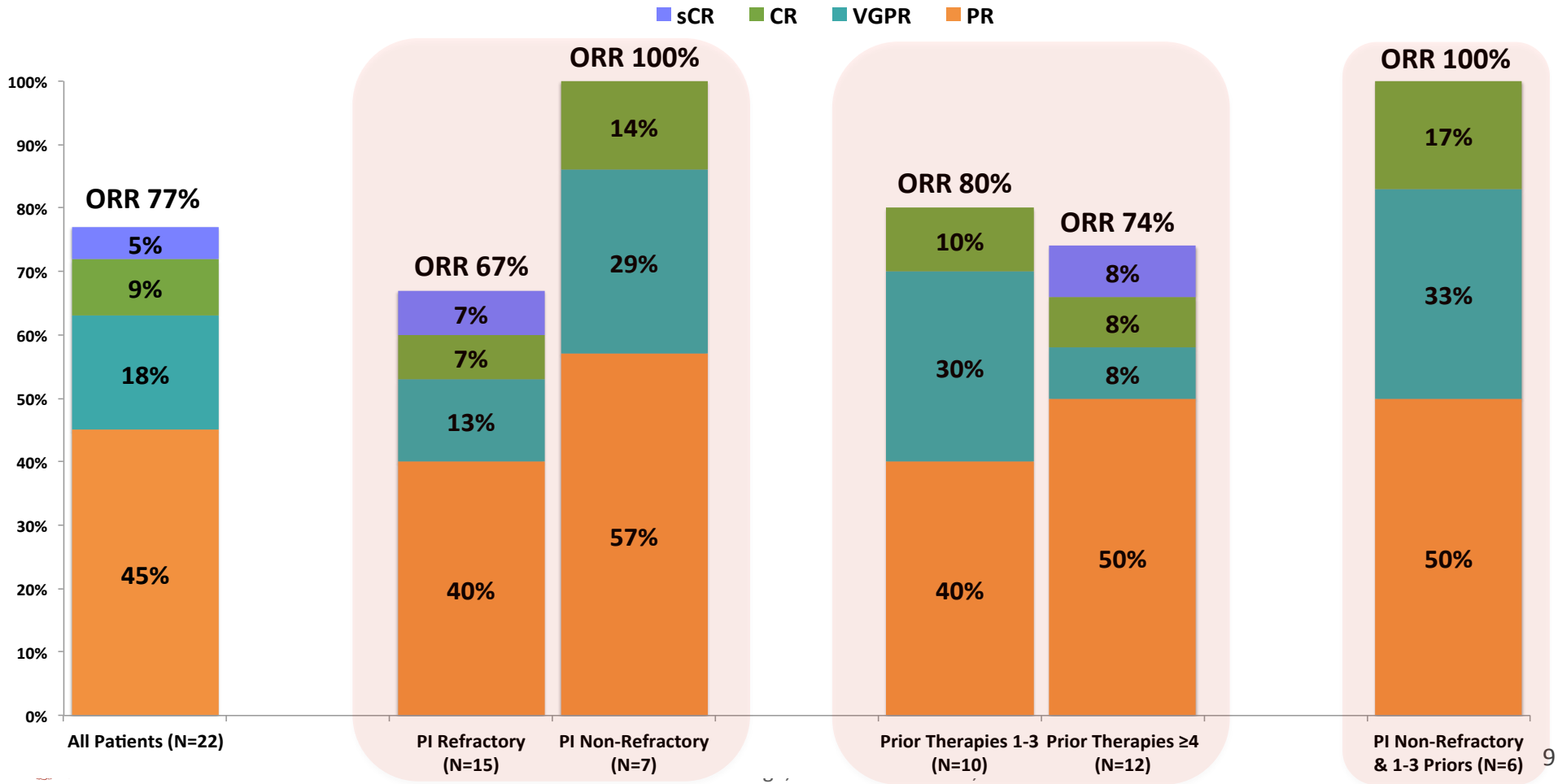
SVd Efficacy – Phase I

Category	N	ORR (%)	CBR (%)	sCR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
Overall	22	17 (77%)	20 (91%)	1 (5%)	2 (9%)	4 (18%)	10 (45%)	3 (14%)	1 (5%)	1 (5%)
PI Refractory	15	10 (67%)	13 (87%)	1 (7%)	1 (7%)	2 (13%)	6 (40%)	3 (20%)	1 (7%)	1 (7%)
PI Non-Refractory*	7	7 (100%)	7 (100%)	--	1 (14%)	2 (29%)	4 (57%)	--	--	--

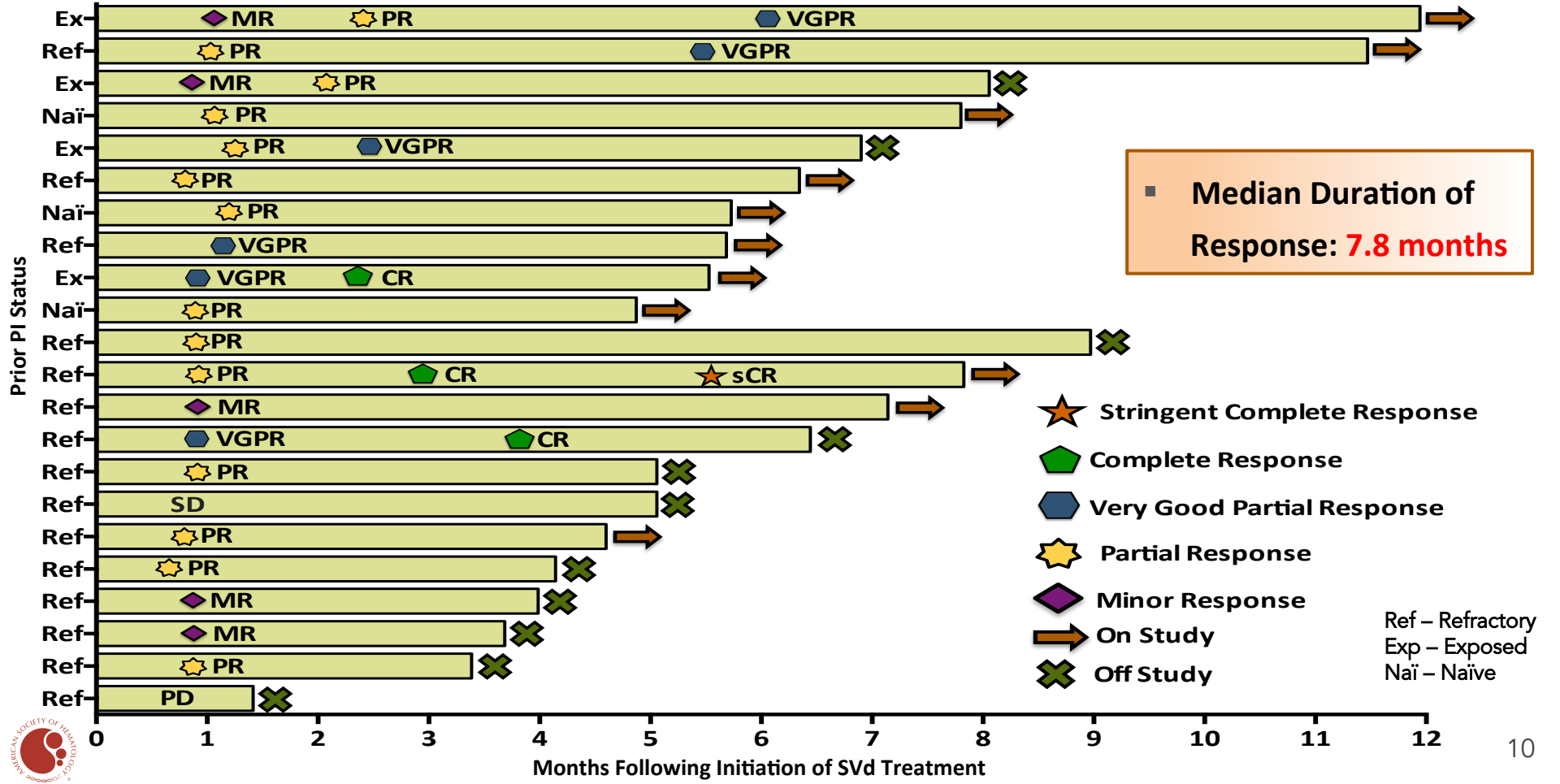
Responses as of November 30, 2016, according to IMWG criteria. ORR=Overall Response Rate (sCR+CR+VGPR+PR), CBR=Clinical Benefit Rate (sCR+CR+VGPR+PR+MR), sCR=Stringent Complete Response, CR=Complete Response, VGPR=Very Good Partial Response, PR=Partial Response, MR=Minor Response, SD=Stable Disease, PD=Progressive Disease

*closest to population to be enrolled in BOSTON Study

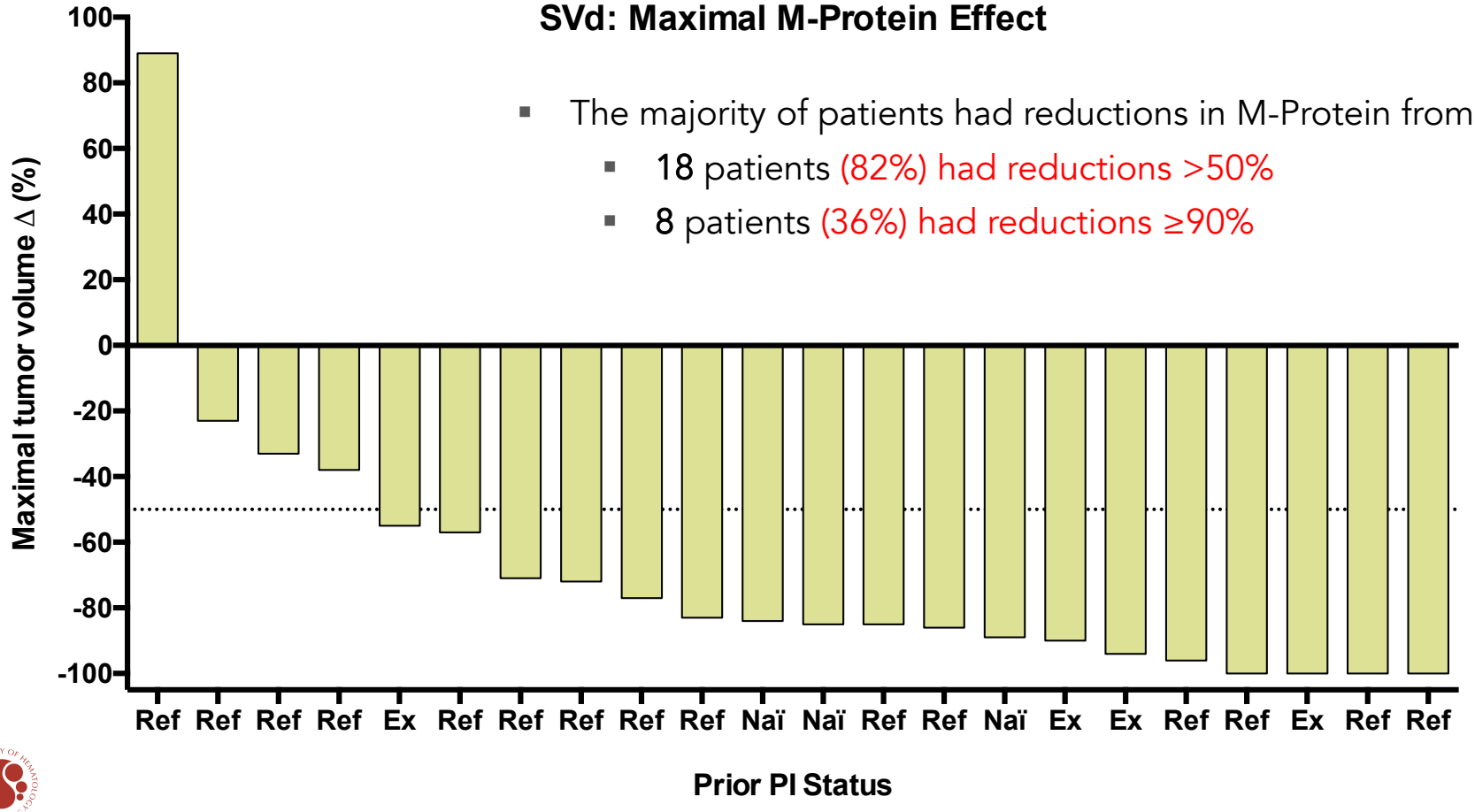
SVd ORR Efficacy: Sub Groups – Phase I



Time on Study and Duration of Response among Responders – Phase I



Change in M-Protein from Baseline – Phase I



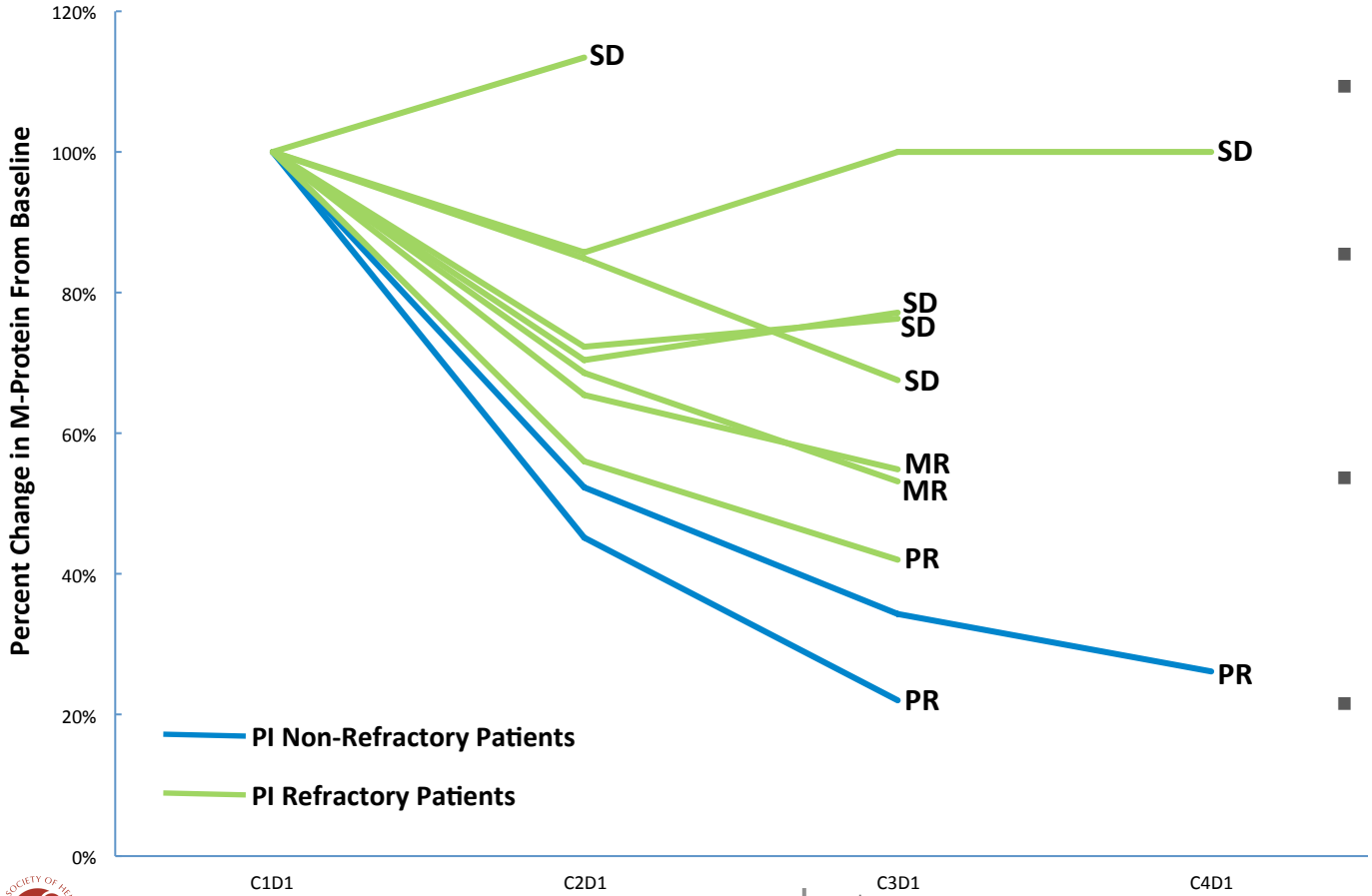
Treatment Related AEs at RP2D

AE Term	100 mg Sel QW + 1.3 mg/m^2 Bort QW RP2D Patients (N=17)				
Gastrointestinal	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Nausea	24%	35%	--	--	**59%**
Anorexia	35%	6%	--	--	**41%**
Vomiting	29%	6%	--	--	**35%**
Diarrhea	18%	--	6%	--	**24%**
Altered Taste	6%	6%	--	--	**12%**
Constitutional					
Fatigue	18%	12%	6%	--	**35%**
Hematologic					
Thrombocytopenia	--	--	6%	12%	**18%**
Other					
Abdominal Pain	6%	--	6%	--	**12%**

- Good tolerability with clear anti-MM activity with once weekly selinexor in combination with once weekly Velcade
- Considering prolonged tolerability and efficacy across all cohorts, the RP2D is:

100 mg oral selinexor QW +
1.3 mg/m^2 bortezomib SC QW x 4 / 5 +
40 mg dexamethasone QW

Expansion Patients – Spider Plot



- Expansion will enroll 20 patients
- 11 patients have been enrolled (10 evaluable for efficacy)
- Median time on study: 3 cycles (range <2 – 4 cycles)
- 9 out of 10 patients remain on treatment

Conclusions

- Selinexor in combination with bortezomib and low dose dexamethasone (SVd) is well tolerated with low rates of major adverse events
  - Minimal clinically significant overlapping toxicity
  - AEs were manageable (predominantly G1/2) and included nausea, fatigue, anorexia, and thrombocytopenia (mostly G3/4).

- SVd has potent activity in patients with heavily pretreated multiple myeloma, including those with proteasome inhibitor (PI)-refractory disease and ≥4 lines of therapy:
  - ORR 77% overall, 67% in PI-refractory disease, and 100% in PI-non-refractory MM

- The recommended SVd phase II dose:
  - *weekly* PO selinexor 100 mg, sc bortezomib 1.3 mg/m^2 and PO dexamethasone 40 mg
  - Convenient, cost-effective and highly potent anti-MM regimen
  - Phase 3 Randomized BOSTON Study of SVd vs. Vd to begin in early 2017