Selinexor and Low Dose Dexamethasone (Sd) in Patients with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib & anti-CD38 mAb Refractory MM: STORM Study

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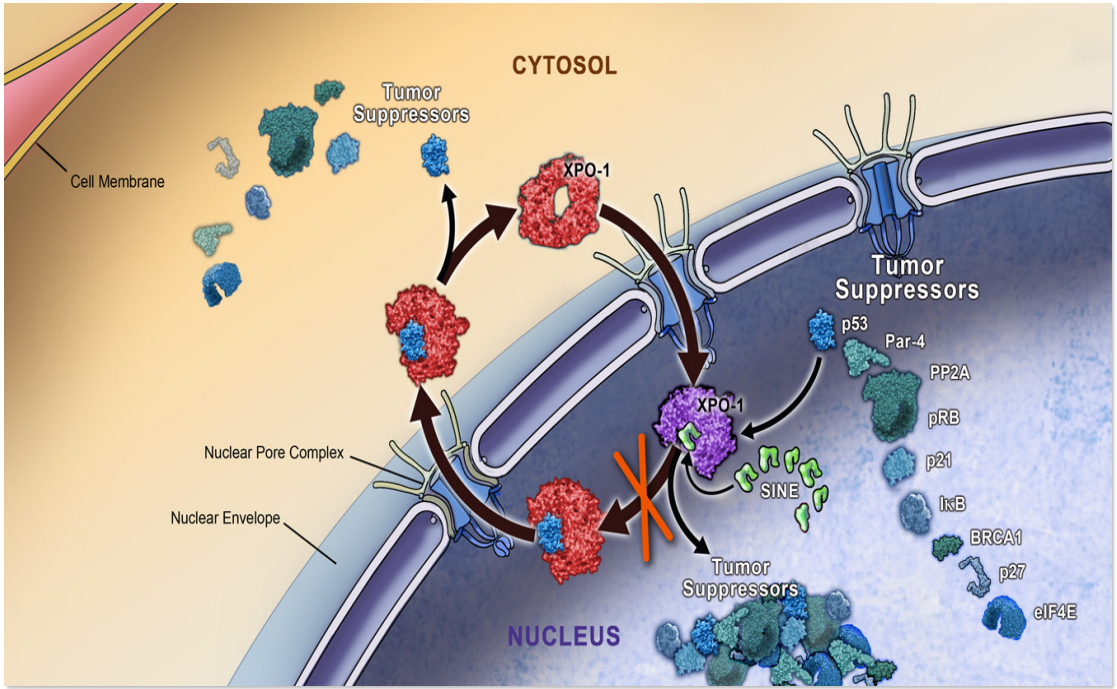
Therapy for Refractory Myeloma

- Patients refractory to bortezomib and lenalidomide:
  - median OS 9 months
  - median PFS 5 months

Kumar, *Leukemia* 2012;26:149–157

- Approvals with single-agent activity in dual-refractory myeloma:
  - 2012: carfilzomib
  - 2013: pomalidomide
  - 2015: daratumumab
- None of these agents are curative

Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression

- In a first-in-human Phase I study, selinexor in combination with dexamethasone showed a 27% ORR in heavily pretreated MM patients

Selinexor **T**reatment of **R**efractory **M**yeloma: **STORM** Phase II Study Design

Inclusion Criteria:

- Patients with **refractory** MM (*≤ 25% response or PD during or within 60 days)*:
  - To most recent anti-MM regimen
  - To bortezomib, carfilzomib, lenalidomide, and pomalidomide ("***Quad*** refractory")
    - Subset also refractory to daratumumab or isatuximab ("***Penta*** refractory")
- Creatinine clearance ≥20 mL/min
- WBC count ≥1500/mm^3, ANC ≥1000/mm^3, Platelet Count ≥75,000/mm^3 (≥30,000/mm^3)

Selinexor **T**reatment of **R**efractory **M**yeloma: **STORM** Phase II Study Design

Primary Endpoint:

- Overall Response Rate (ORR): Stringent Complete Response (sCR) + Complete Response (CR) + Very Good Partial Response (VGPR) + Partial Response (PR)

Treatment: Selinexor 80 mg + dexamethasone 20 mg, twice weekly

- Group 1: 6 doses / 28 day cycle (3 weeks on, 1 week off)
- Group 2: 8 doses / 28 day cycle (4 weeks continuously)

Selinexor Dose Modifications for Toxicity:

- Reduction to 60 mg twice weekly
- Reduction to 80 mg once weekly for thrombocytopenia or fatigue
- Short interruptions also utilized

STORM – Patient Characteristics

STORM Patient Characteristics	Quad Refractory	Penta Refractory
Patients Enrolled as of November 1, 2016	**48**	**31**
Median Age, Years (range)	62 (41 –78)	68 (34 – 78)
Males : Females	24 (50%) : 24 (50%)	13 (42%) : 18 (58%)
Median Prior Regimens (range)	7 (3 – 16)	7 (5 – 17)
Median Years from Diagnosis (range)	4 years (1 – 16)	4 years (<1 – 35)
Prior Therapies		
Glucocorticoid	48 (100%)	31 (100%)
Alkylating Agents	47 (98%)	30 (97%)
Stem Cell Transplant	37 (77%)	24 (77%)
Anthracyclines	20 (42%)	12 (39%)
Patients treated with 6 doses : 8 doses / cycle	40 (83%) : 8 (17%)	11 (35%) : 20 (65%)

Treatment Related Adverse Events ≥10%

AE Term	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=79)
Gastrointestinal					
Nausea	41%	25%	8%	--	**73%**
Anorexia	19%	28%	3%	--	**49%**
Vomiting	30%	10%	4%	--	**44%**
Diarrhea	34%	4%	5%	--	**43%**
Dehydration	1%	8%	3%	--	**11%**
Dysgeusia	6%	5%	--	--	**11%**
Constitutional					
Fatigue	15%	33%	15%	--	**63%**
Weight Loss	19%	13%	1%	--	**33%**
Hematologic					
Thrombocytopenia	6%	8%	25%	34%	**73%**
Anemia	3%	19%	27%	1%	**49%**
Leukopenia	4%	14%	13%	1%	**32%**
Neutropenia	3%	4%	11%	6%	**24%**
Lymphopenia	--	4%	9%	1%	**14%**
Other					
Hyponatremia	20%	--	22%	--	**42%**
CPK Increase	3%	5%	3%	--	**10%**
Dizziness	9%	1%	--	--	**10%**
Fever	6%	3%	1%	--	**10%**

Selinexor Dose Modifications:

- Interruptions:
  41 patients (52%)
- Reductions:
  29 patients (37%)
- Discontinuation:
  14 patients (18%)

Supportive Care:

- Antiemetics
- Appetite stimulants
- Hematopoietic growth factors
- Thrombopoietin receptor agonists
- Salt supplementation

Independent Review Committee (IRC) Assessed Efficacy

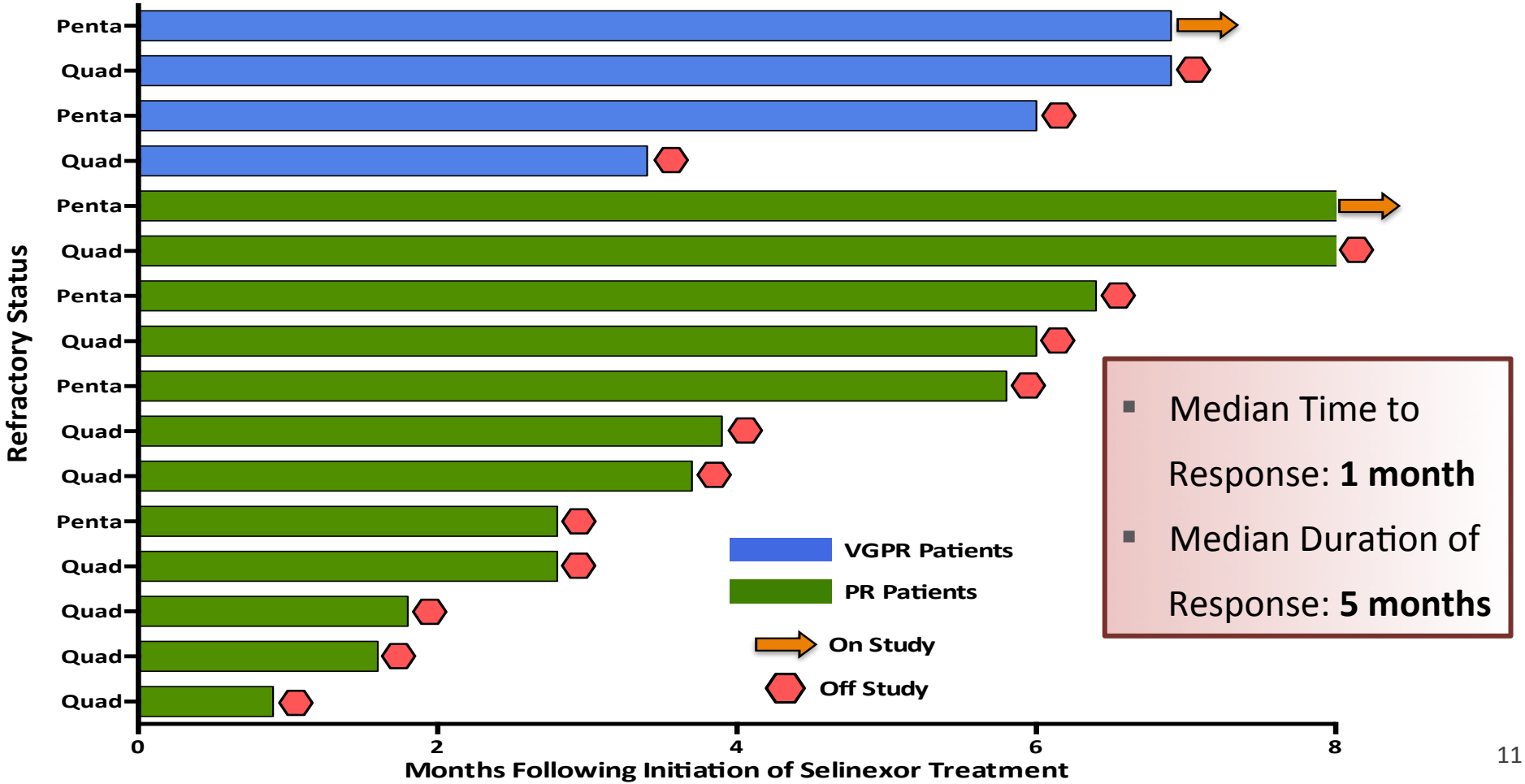
Category	N*	ORR (%)	CBR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)	NE (%)
Overall	78	**16 (21%)**	26 (33%)	4 (5%)	12 (15%)	10 (13%)	27 (35%)	9 (12%)	16 (21%)
Quad Refractory	48	**10 (21%)**	14 (29%)	2 (4%)	8 (17%)	4 (8%)	21 (44%)	4 (8%)	9 (19%)
Penta Refractory	30	**6 (20%)**	12 (40%)	2 (7%)	4 (13%)	6 (20%)	6 (20%)	5 (17%)	7 (23%)
6 Doses / Month	51	**10 (20%)**	15 (29%)	3 (6%)	7 (14%)	5 (10%)	21 (41%)	4 (8%)	11 (22%)
8 Doses / Month	27	**6 (22%)**	11 (41%)	1 (4%)	5 (19%)	5 (19%)	6 (22%)	5 (19%)	5 (19%)

*1 patient did not have measurable disease at baseline

High Risk Cytogenetics: Efficacy

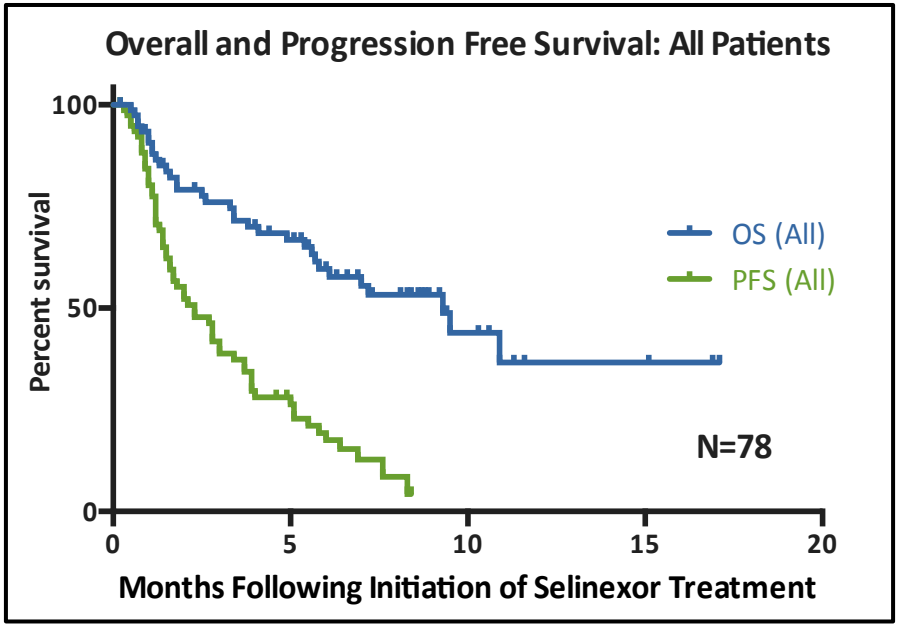
Category	N	ORR (%)	CBR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
Standard Risk	22	**4 (18%)**	9 (41%)	1 (5%)	3 (14%)	5 (23%)	11 (50%)	2 (9%)
All High Risk	17	**6 (35%)**	9 (53%)	1 (6%)	5 (29%)	3 (18%)	6 (35%)	2 (12%)
del(17p)	8	**3 (38%)**	5 (63%)	1 (13%)	2 (25%)	2 (25%)	2 (25%)	1 (13%)
t(4;14)	4	**2 (50%)**	2 (50%)	--	2 (50%)	--	2 (50%)	--
t(14;16)	1	**1 (100%)**	1 (100%)	--	1 (100%)	--	--	--
del(17p) & t(4;14)	3	**--**	1 (33%)	--	--	1 (33%)	2 (67%)	--
del(17p) & t(14;16)	1	**--**	--	--	--	--	--	1 (100%)

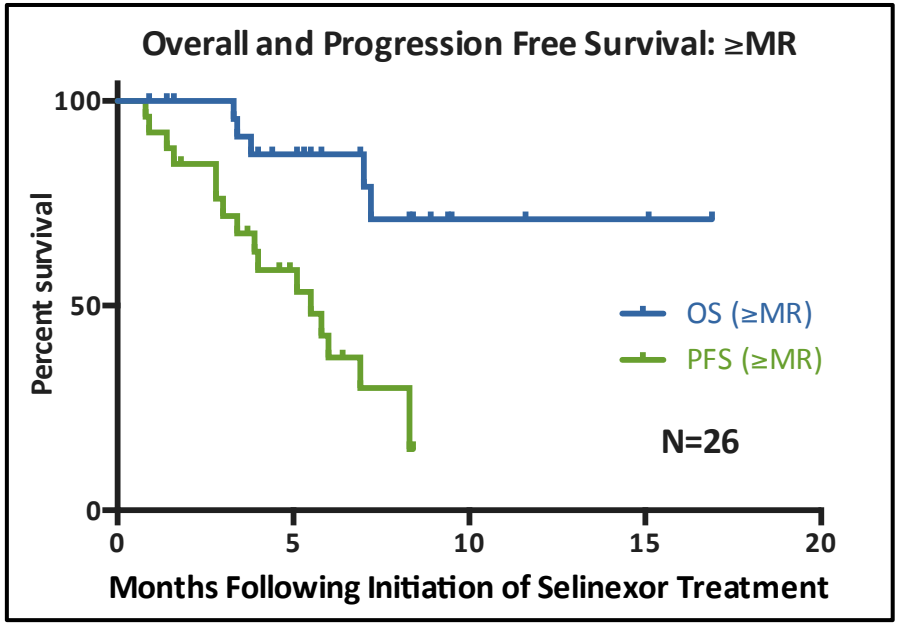
Time on Study & Duration of Response Among Responders



- Median Time to Response: **1 month**
- Median Duration of Response: **5 months**

Overall and Progression Free Survival





Category	All Patients (N=78)	≥ MR (N=26)
Median OS	9.3 Months	Not Reached
Median PFS	2.3 Months	5.5 Months

Conclusions

- Penta refractory myeloma represents an unmet medical need
- Selinexor in combination with low dose dexamethasone (Sd) has encouraging activity in patients with quad and penta refractory multiple myeloma
  - ORR 21%
  - Median duration of response 5 months
  - Similar response rate in patients with high-risk cytogenetic abnormalities
- AEs were primarily nausea, anorexia, fatigue, thrombocytopenia, and anemia
  - Treatment experience has resulted in improved strategies for adverse event management
- An expansion is underway including 122 patients with penta refractory myeloma treated with 8 doses / cycle