Efficacy of Oral Selinexor plus Low Dose Dexamethasone (Sd) in Patients with Penta-Refractory Myeloma: Results of the Pivotal STORM Part II Study

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Disclosures

Research Support:	Karyopharm, Janssen, Celgene, Amgen, GSK
Consultant	n/a
Honoraria	Karyopharm, Janssen, Celgene, GSK
Scientific Advisory Board	Janssen, Celgene, Amgen, GSK
Major Stockholder	n/a
Employee, Speakers Bureau	n/a

Acknowledgments

Patients, their families, and caregivers

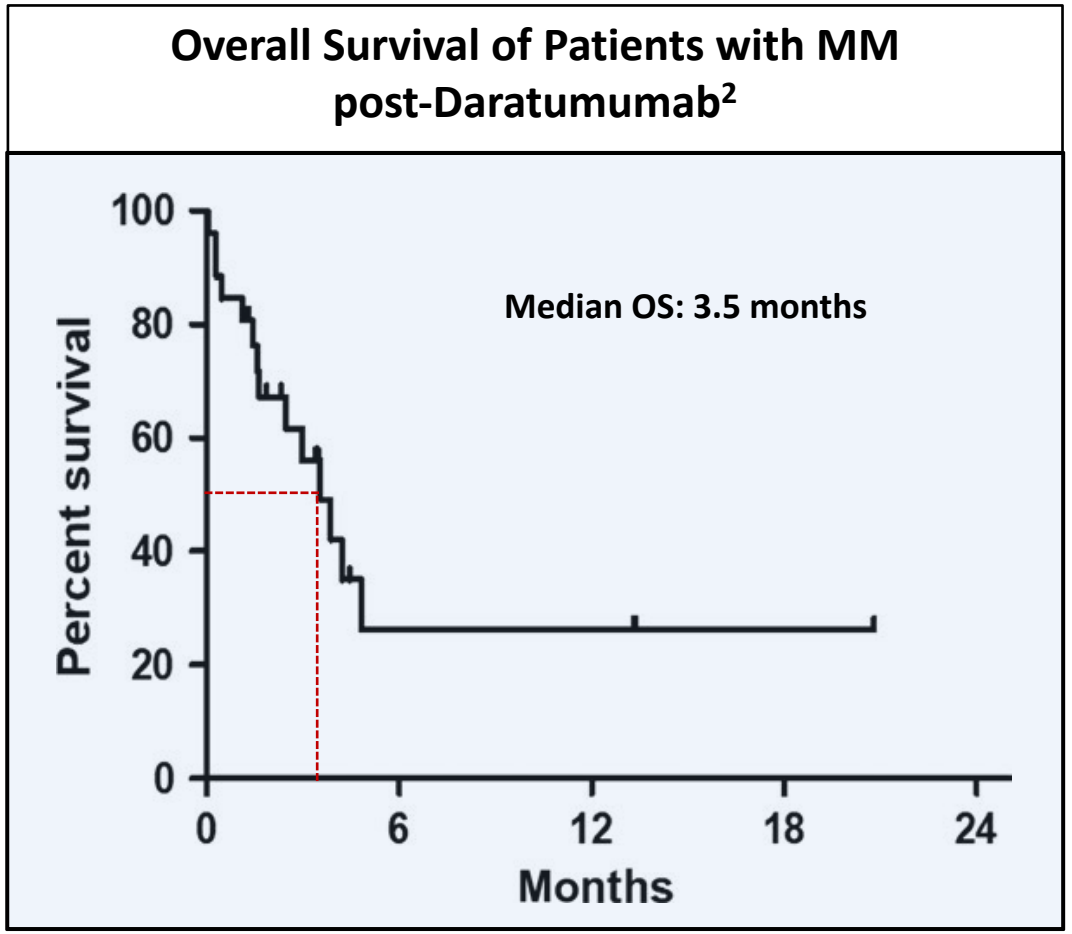
Investigators, co-investigators and study teams at each participating center

- Icahn School of Medicine at Mount Sinai, New York, NY
- Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA
- National and Kapodistrian University of Athens, Athens, Greece
- Winship Cancer Center at Emory University, Atlanta, GA
- Kimmel Cancer Center at John Hopkins, Baltimore, MD
- Nantes University Hospital Center, Nantes, France
- University of Michigan, Ann Arbor, MI
- Dana Farber Cancer Institute, Boston, MA
- John Therurer Cancer Center at Hackensack University, Hackensack, NJ
- Mayo Clinic Rochester, Rochester, NY
- Siteman Cancer Center at Washington University, St. Louis, MO
- University of North Carolina, Chapel Hill, NC
- Heidelberg University Hospital, Heidelberg, Germany
- University Hospital of Tübingen, Tübingen, Germany
- University Hospital Leuven, Leuven, Belgium
- Perlmutter Cancer Center at NYU, New York, NY
- Ingram Cancer Center at Vanderbilt University, Nashville, TN
- Mayo Clinic Arizona, Scottsdale, AZ
- Sylvester Comprehensive Cancer Center at University of Miami
- University of Alabama, Birmingham, AL
- Yale University, New Haven, CT
- Baylor University, Dallas, TX
- University Hospital Wuerzburg, Wuerzburg, Germany
- Institut Jules Bordet, Brussels, Belgium
- Necker Children's Hospital, Paris, France
- Hopital Saint Antoine, Paris, France
- La Pitie-Salpetriere University Hospital, Paris, France
- Massachusetts General Hospital, Boston, MA

This study was sponsored by Karyopharm Therapeutics

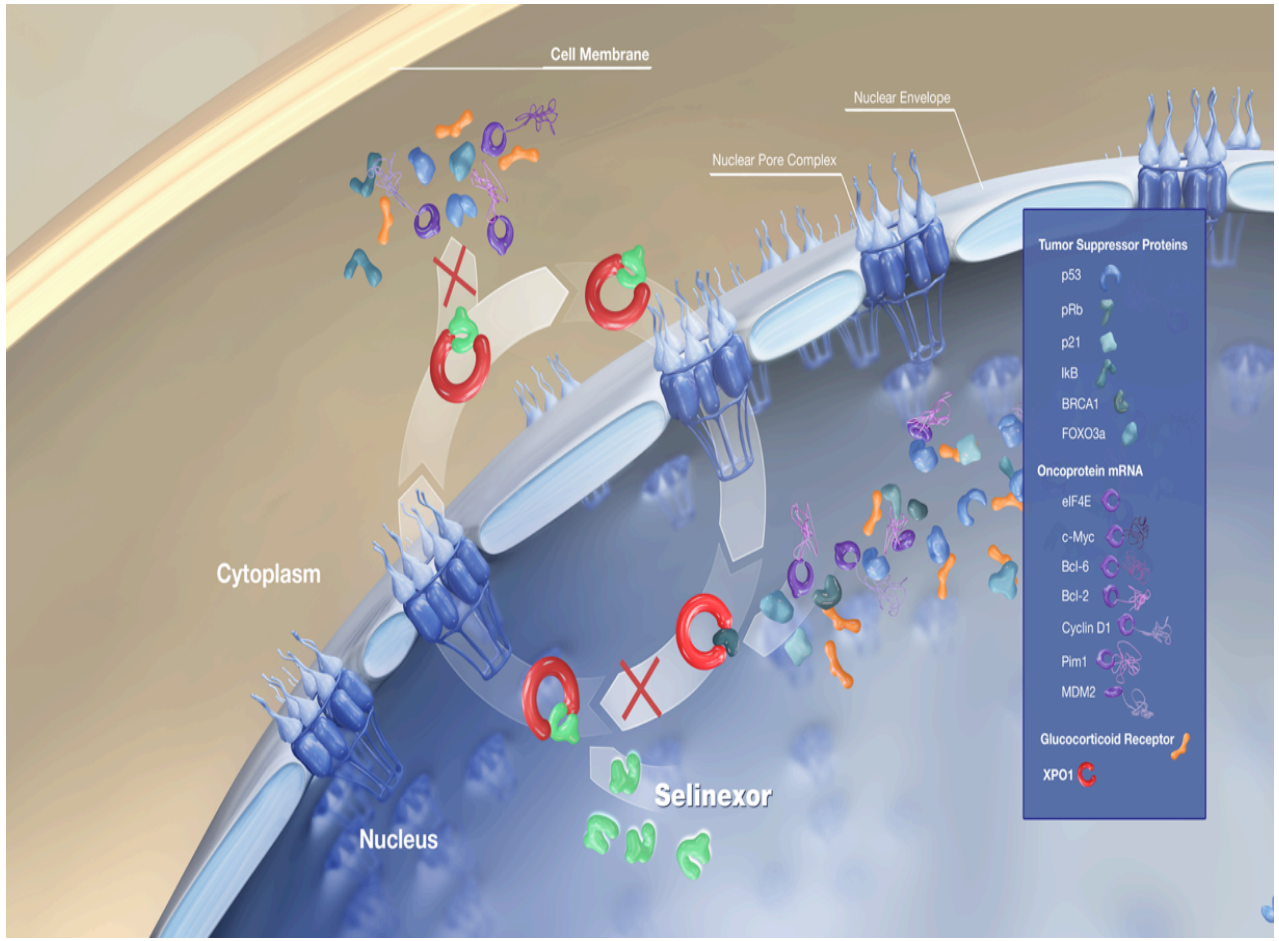
Background: Penta-Refractory Myeloma

- Multiple myeloma (MM) remains largely incurable despite novel therapies; ~13,000 deaths anticipated in USA in 2018[1]
- With increased use of novel agents, a growing number of patients are exposed to bortezomib(B), carfilzomib(C), lenalidomide(L), pomalidomide(P) and daratumumab(D) and developing MM refractory to PIs, IMiDs, and daratumumab
- There are no approved drugs with established clinical activity in penta-refractory MM
- **Patients with penta-refractory MM have poor overall survival, estimated at 3.5 months[2], representing a high unmet medical need**



[1] *Cancer Facts and Figures, ACS. 2018*
[2] *Pick et al. Eur J Haematol. 2018;100:494*

Selinexor:
First in Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-3]



[1]Schmidt et al., Leukemia, 2013, [2]Tai et al., Leukemia, 2013, [3]Argueta et al., Oncotarget, 2018

Exportin 1 (XPO1) is the major nuclear export protein for:

- Tumor suppressor proteins (TSPs, e.g p53, IκB and FOXO)
- Glucocorticoid receptor (GR)
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, BCL-xL, cyclins)

XPO1 is overexpressed in MM:

- High **XPO1** levels enable cancer cells to escape TSP mediated cell cycle arrest and induction of apoptosis
- **XPO1** levels correlate with poor prognosis and drug resistance

Selinexor is an oral selective **XPO1** inhibitor; preclinical data supports that selinexor :

- Reactivates multiple TSPs relevant to MM, inhibits NF-κB signaling and reduces c-Myc levels
- In combination with dexamethasone (dex) reactivates GR signaling

Selinexor + Dexamethasone:
Initial Clinical Data in RRMM

Phase 1 Clinical Trial of Selinexor (Chen et al, Blood 2017) (N=81 patients):

- Enrolled patients with heavily pretreated MM
- R2PD was Selinexor 45 mg/m^2 (~80 mg) and dex (20 mg) given twice weekly
- The combination demonstrated an ORR of 50% (n=12 patients)

Phase 2b STORM Clinical Trial Part 1 (Vogl et al, JCO 2018) (N=79 patients)

- Enrolled both quad- (B,C,L,P) or penta-refractory (B,C,L,P, anti-CD38) MM
- Selinexor/dexamethasone was administered either 3/4 or 4/4 weeks
- Main side effects: nausea, anorexia, fatigue, thrombocytopenia, hyponatremia, and anemia
- Overall response rate (ORR) of 21%

Pivotal STORM Part II: Study Design

Oral Selinexor | 80 mg + **Dexamethasone** | 20 mg

- Selinexor / dexamethasone twice weekly (Days 1 and 3) until Disease Progression

Patient Population:

- MM previously treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, an alkylator, and glucocorticoids.
- Disease documented to be refractory to ≥1 PI, ≥1 IMiD, daratumumab, glucocorticoid and last line of therapy

Primary Endpoint:

Overall Response rate: ORR

Secondary Endpoints:

Duration of Response (DOR),
Clinical benefit rate (CBR),
Overall survival (OS),
Progression free survival (PFS)
Safety

Key Inclusion/Exclusion:

- Creatinine clearance ≥ 20 mL/min
- ANC ≥ 1,000/mm^3,
- Platelets ≥ 75,000/mm^3 (if bone marrow plasma cell > 50%; plt > 50,000/mm^3
- Hemoglobin ≥ 8.5 g/dL

Pivotal STORM Part II: Patient Characteristics

	N=122*
Age, years median (range)	65 (40 – 86)
Time from Diagnosis, Years median (range)	6.6 (1.1 – 23.4)
Males : Females	71 M (58%) : 51 F (42%)
Creatinine Clearance < 60 mL/min	40 (32%)
High Risk Cytogenetics: (del17p, t(4;14), t(14;16), 1q21)	65 (53%)
MM Subtype: FLC	35 (29%)
ECOG Performance Status: 0 / 1 / 2 / Unk	30% / 58% / 9% / 2%
Revised International Staging System (R-ISS): I / II / III / Unk	16% / 64% / 19% / <1%

*A total of 123 patients were enrolled, however 1 patient did not meet eligibility criteria, thus was excluded from this analysis

Pivotal STORM Part II: Prior Therapies

	N=122
Median Prior Regimens (range)	**7 (3 – 18)**
Number of Prior Treatment Regimens	
≤6	48 (39%)
7–8	38 (31%)
≥9	36 (30%)
Prior Treatments	
-Refractory to PI / IMiD / Daratumumab / Glucocorticoid	122 (100%)
-Refractory to Carfilzomib/Pomalidomide/Daratumumab	117 (96%)
-Refractory to 2 PIs / 2 IMiDs / Daratumumab	83 (68%)
-Stem Cell Transplant	102 (84%)
- ≥2 Transplants	29 (28%)
-Intensive Combination Chemotherapy (e.g. DT-PACE)	32 (26%)
-Daratumumab in Last Prior Regimen	58 (48%)
-Daratumumab in Combination	86 (70%)
-CAR-T Cell Therapy	2 (2%)

Pivotal STORM Part II:

Treatment Related Non-Hematological Adverse Events in ≥10% of Patients

Gastrointestinal Disorders	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=122)
Nausea	32 (26.0%)	41 (33.3%)	12 (9.8%)	--	**85 (69.1%)**
Anorexia	19 (15.4%)	41 (33.3%)	4 (3.3%)	--	**64 (52.0%)**
Vomiting	18 (14.6%)	21 (17.1%)	4 (3.3%)	--	**43 (35.0%)**
Diarrhea	21 (17.1%)	12 (9.8%)	8 (6.5%)	--	**41 (33.3%)**
Altered Taste	7 (5.7%)	5 (4.1%)	--	--	**12 (9.8%)**
Constipation	8 (6.5%)	3 (2.4%)	1 (0.8%)	--	**12 (9.8%)**
Constitutional					
Fatigue/Asthenia	16 (13.0%)	42 (34.1%)	28 (22.8%)	--	**86 (69.9%)**
Weight Loss	31 (25.2%)	26 (21.1%)	1 (0.8%)	--	**58 (47.2%)**
Dizziness	10 (8.1%)	3 (2.4%)	--	--	**13 (10.6%)**
Other					
Hyponatremia	18 (14.6%)	--	20 (16.3%)	--	**38 (30.9%)**
Insomnia	8 (6.5%)	3 (2.4%)	2 (1.6%)	--	**13 (10.6%)**
Pneumonia[1]	--	2 (1.6%)	3 (2.4%)	--	**6 (4.9%)**
Sepsis[2]	--	--	--	1 (0.8%)	**2 (1.6%)**

[1]Pneumonia – 1 Grade 5 Event [2]Sepsis – 1 Grade 5 Event

Safety data cutoff of August 17, 2018; executed on 02-Sept-2018

Pivotal STORM Part II:

Treatment Related Hematological Adverse Events in ≥10% of Patients

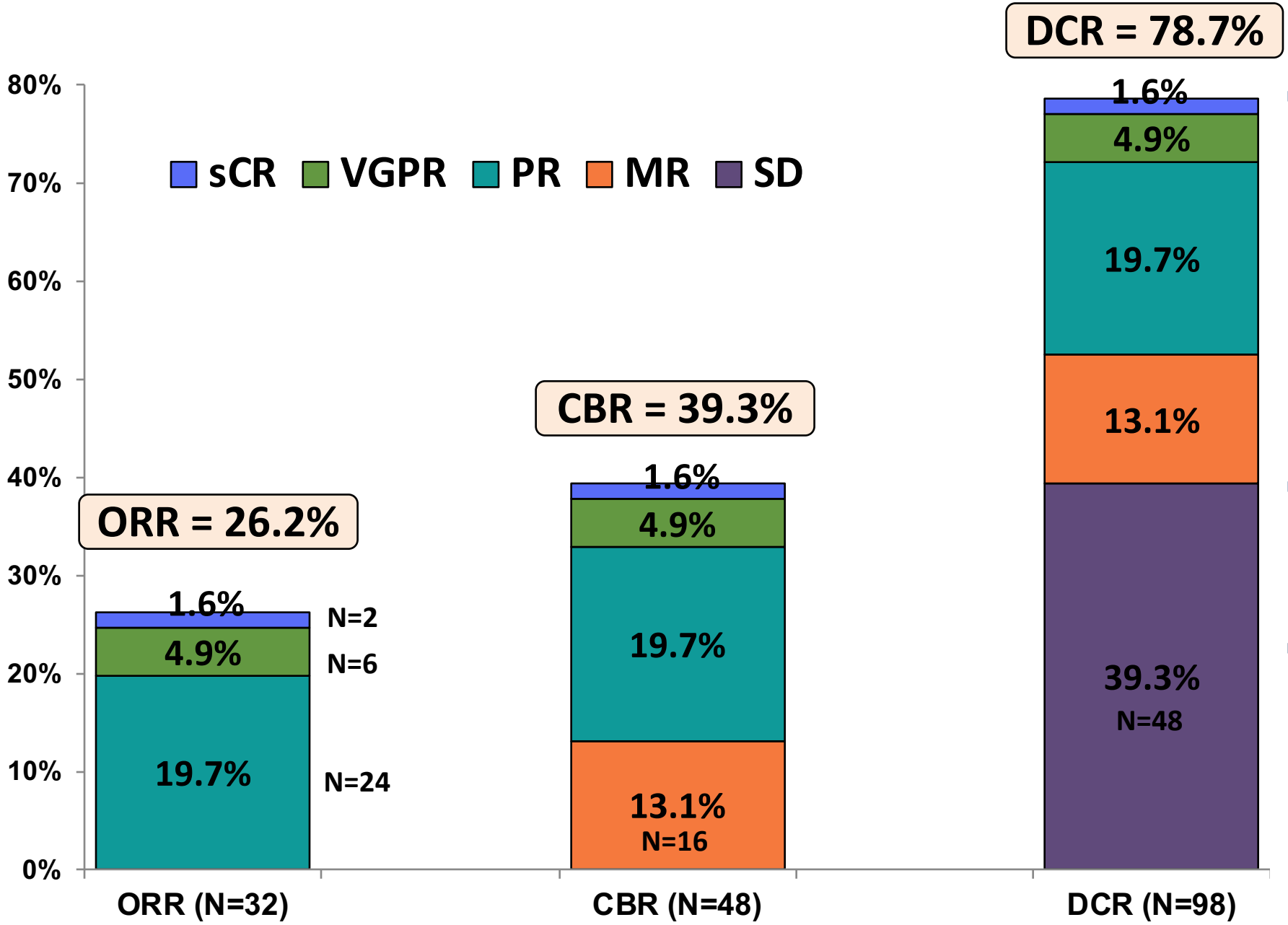
Adverse Event Term	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=122)
Thrombocytopenia	10 (8.1%)	7 (5.7%)	28 (22.8%)	38 (30.9%)	**83 (67.5%)**
Anemia	5 (4.1%)	18 (14.6%)	35 (28.5%)	1 (0.8%)	**59 (48.0%)**
Neutropenia*	6 (4.9%)	16 (13.0%)	18 (14.6%)	4 (3.3%)	**44 (35.8%)**
Leukopenia	6 (4.9%)	13 (10.6%)	17 (13.8%)	--	**36 (29.3%)**
Lymphopenia	2 (1.6%)	4 (3.3%)	8 (6.5%)	3 (2.4%)	**17 (13.8%)**

*Febrile Neutropenia (Grade 3) in 2 patients (1.6%)

23 patients (19.5%) discontinued due to treatment related AE

Safety data cutoff of August 17, 2018; executed on 02-Sept-2018

Pivotal STORM Part II: Efficacy

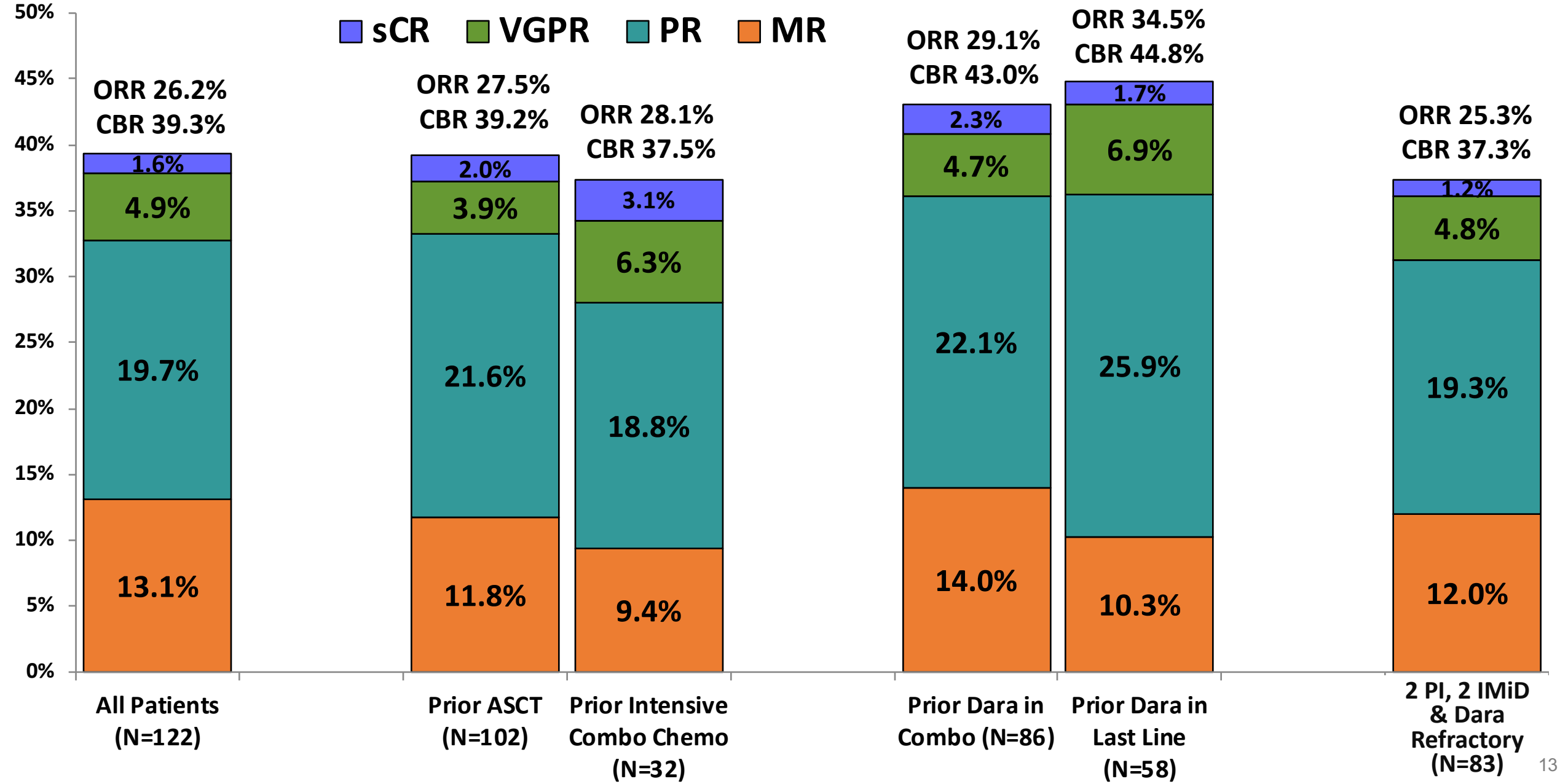


- In penta-refractory MM patients with a median of 7 prior treatment regimens, **ORR of 26.2%,** including **2 stringent CRs**
  - **sCRs were MRD negative** at 10^{-6} and 10^{-4}
- Median time to response was **1 month** (range 1 to 14 weeks)
- 16 patients (13.1%) progressed (PD) on therapy and 10 patients (8.2%) were not evaluable for response

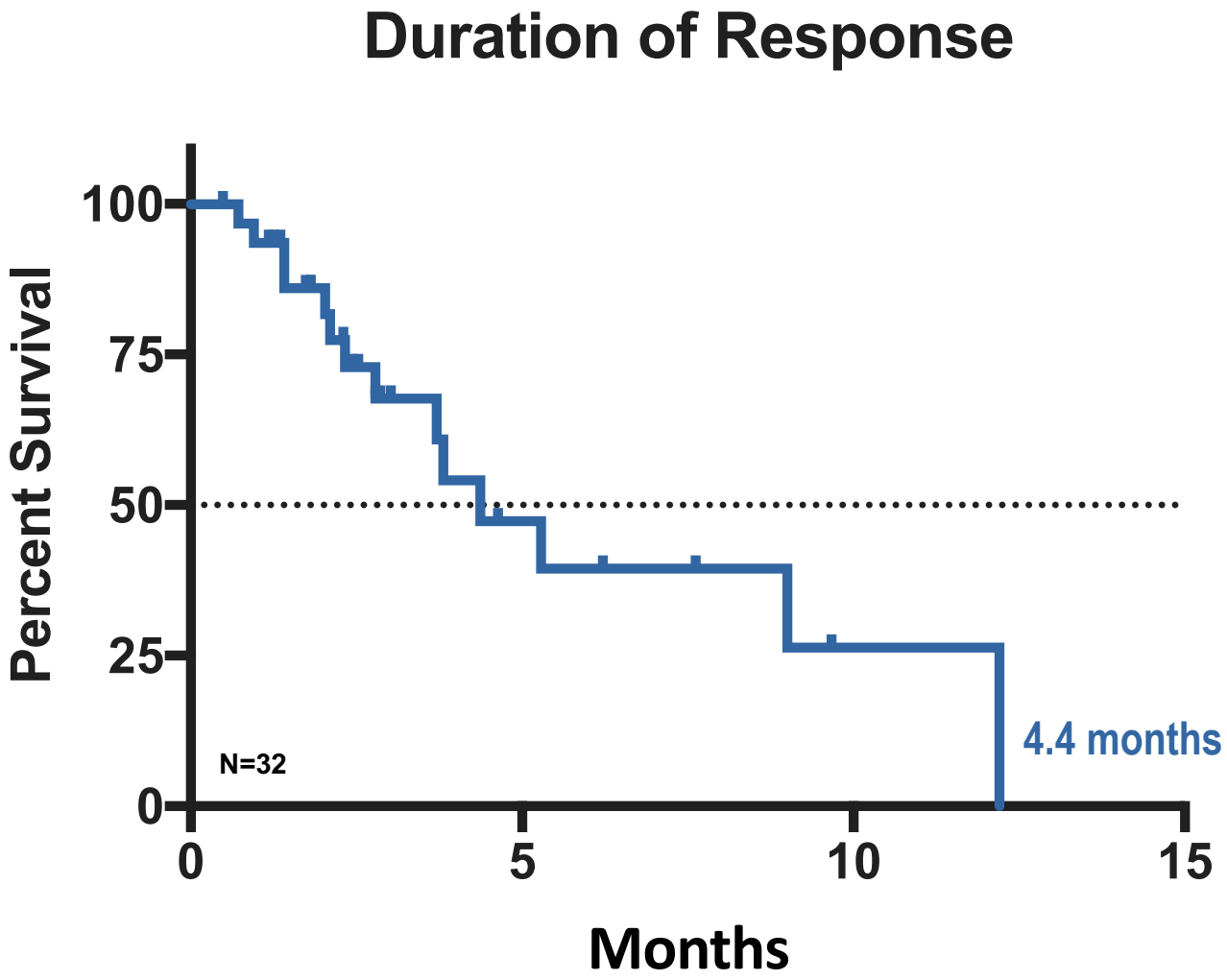
Responses as of August 17, 2018 were adjudicated according to the IMWG criteria *(Kumar, 2016)* by an independent review committee (IRC).

DCR=Disease Control Rate (sCR+VGPR+PR+MR+SD)

Pivotal STORM Part II: Efficacy Sub-Groups

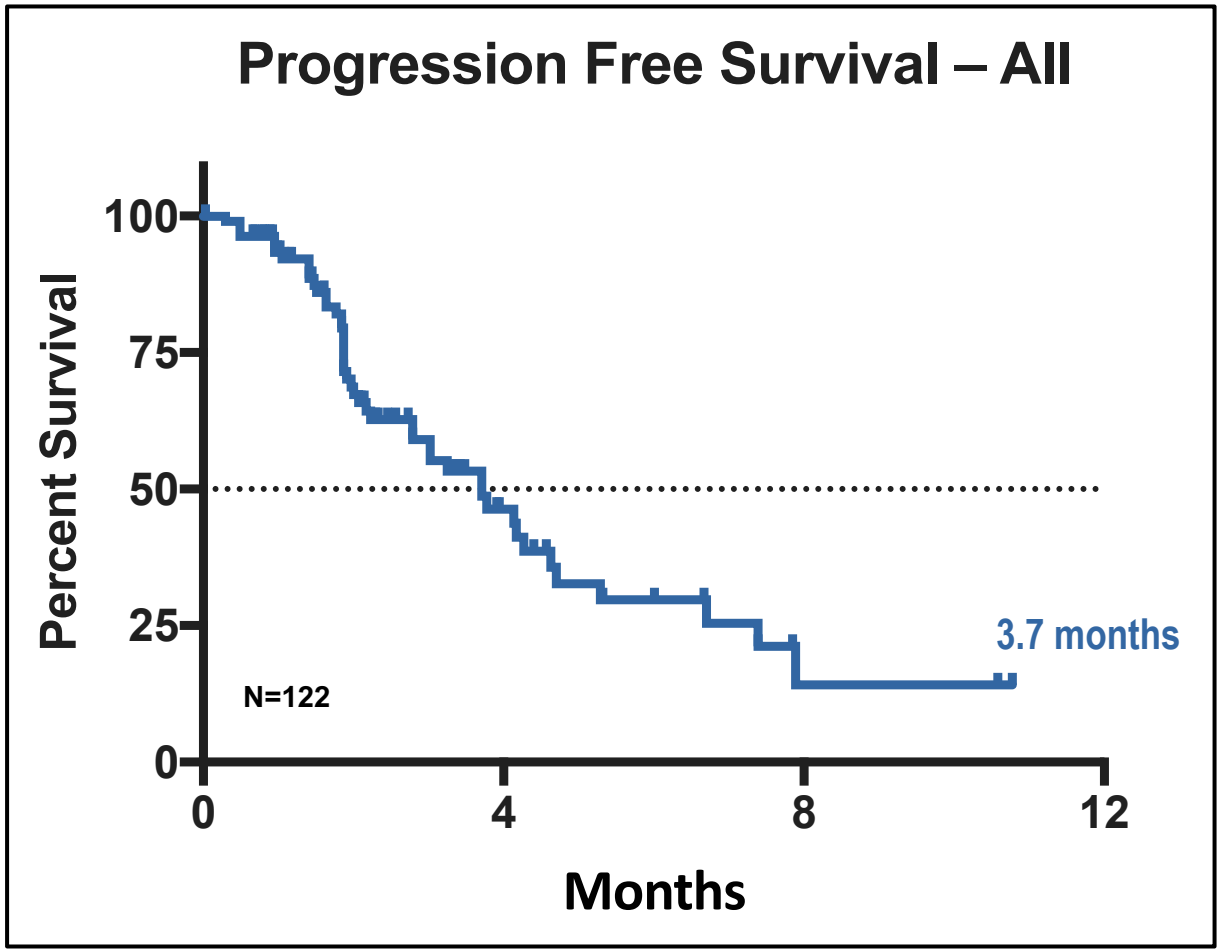


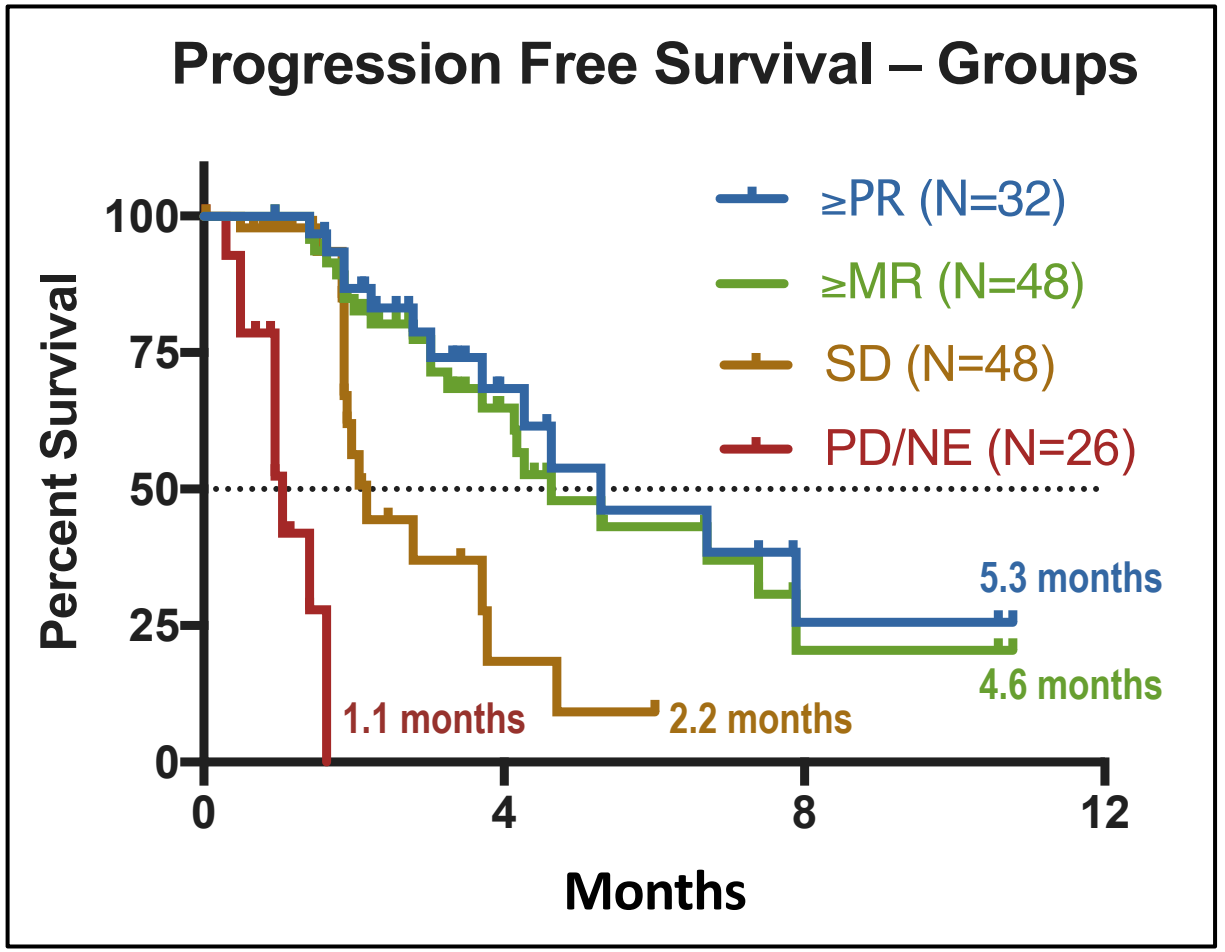
Pivotal STORM Part II: Duration of Response (patients ≥PR)



- The median duration of response is **4.4 months** ranging (<1 – 12.2 months)
- Responses typically occurred within the first cycle (4 weeks) of treatment with Sd

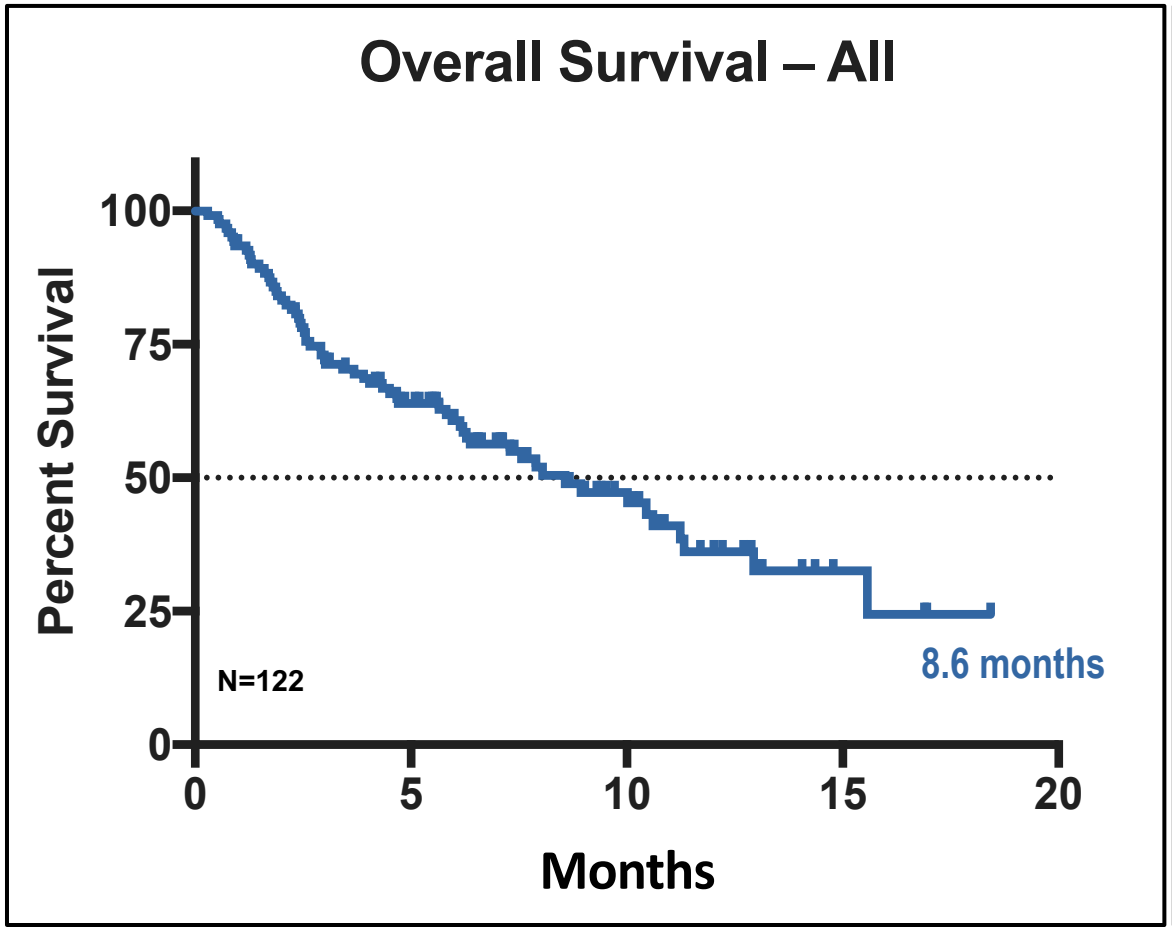
Pivotal STORM Part II: Progression Free Survival

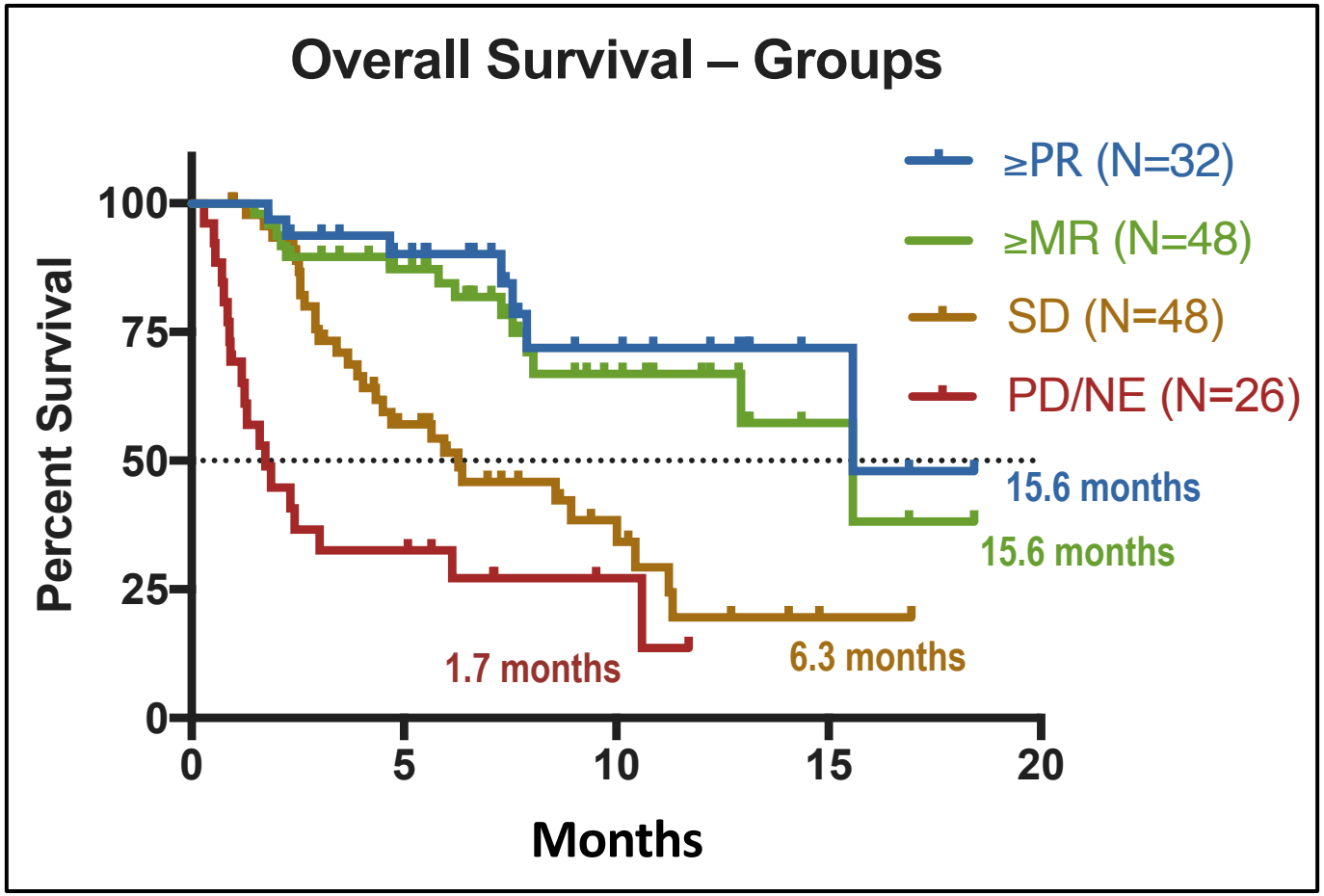




Category	All Patients (N=122)	≥ PR (N=32)	≥ MR (N=48)	SD (N=48)	PD/NE (N=26)
Median PFS	3.7 Months	5.3 Months	4.6 Months	2.2 Months	1.1 Months

Pivotal STORM Part II: Overall Survival





Category	All Patients (N=122)	≥ PR (N=32)	≥ MR (N=48)	SD (N=48)	PD/NE (N=26)
Median OS	8.6 Months	15.6 Months	15.6 Months	6.3 Months	1.7 Months

Pivotal STORM Part II: Conclusions

- **Selinexor plus dexamethasone** is an all-oral, first in class investigational treatment with a novel mechanism of action
- Most important G3/4 AEs: thrombocytopenia (53.7%); anemia (29.3%); fatigue (22.8%); hyponatremia (16.3%); nausea (9.8%); diarrhea (6.5%); anorexia (3.3%), emesis (3.3%)
- **Selinexor plus dexamethasone achieved:**
  - **ORR of 26.2% in Penta–Refractory Myeloma**
  - Duration of Response **4.4 months**
  - Clinical Benefit Rate of **39.3%**; Disease Control Rate (≥SD) of **78.7%**
  - 2 patients achieved sCRs: both **MRD negative**
  - Each of the 2 patients with relapse after CAR-T therapy achieved a PR
- **Median OS**: **8.6 months**; **15.6 months** in pts that achieved ≥MR; **1.7 months** in pts with PD/NE