Results of the Pivotal STORM Study (Part 2): Deep and Durable Responses with Oral Selinexor plus Low Dose Dexamethasone in Patients with Penta-Exposed and Triple Class Refractory MM

A. Chari, DT. Vogl, MA. Dimopoulos, A. Nooka, C. Huff, P. Moreau, C. Cole, J. Richter, D. Dingli, R. Vij, S. Tuchman, M. Raab, K. Weisel, M. Delforge, D. Kaminetzky, RF. Cornell, AK. Stewart, J. Hoffman, KN. Godby, TL. Parker, M. Levy, M. Schreder, N. Meuleman, L. Frenzel, M. Mohty, S. Choquet, A. Yee, M. Gavriatopoulou, LJ. Costa, J. Shah, C. Picklesimer, JR. Saint-Martin, L. Li, MG. Kauffman, S. Shacham, P. Richardson, S. Jagannath

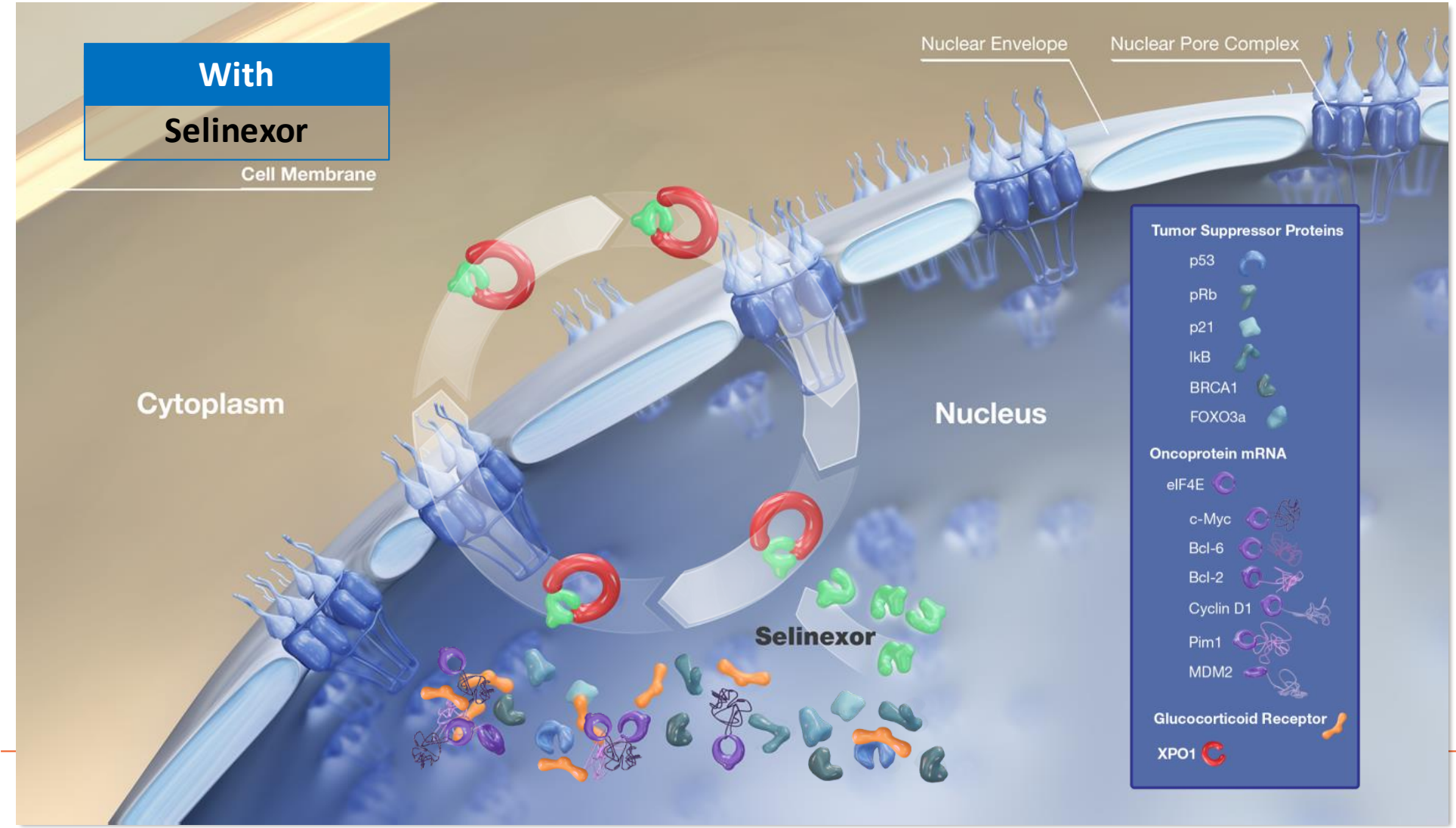
Background: Triple Class Refractory Myeloma and Selinexor

- Multiple myeloma (MM) remains largely incurable despite novel therapies; ~13,000 deaths anticipated in USA in 2018[1]
- A growing number of patients are exposed to the proteasome inhibitors (PIs) bortezomib and carfilzomib, the immunomodulatory (IMiDs) agents lenalidomide and pomalidomide, and the anti-CD38 monoclonal antibody daratumumab
- Eventually patients develop penta-exposed and triple class refractory MM (refractory to PIs, IMiDs, and daratumumab) and have a dismal prognosis with a median overall survival as short as 1.3 to 3.5 months[2, 3]
- There are no approved drugs with established clinical activity in triple class refractory MM
- In a Phase 1 dose-escalation study[4], selinexor 3-60 mg/m^2 without dex had limited activity; 45 mg/m^2 (~80 mg) + dex 20 mg twice weekly was associated with 50% ORR (n=12, not dara-exposed nor quad-refractory)
- In a Phase 2b study[5] of selinexor 80 mg + dex 20 mg twice weekly, ORR was 21% (n=78)
  - Quad- and penta-refractory with both 3/4 week and 4/4 week dosing

PIs=Proteasome Inhibitors; IMiDs=Immunomodulatory Drugs; OS=Overall Survival; ORR=Overall Response Rate.

[1] *Cancer Facts and Figures, ACS. 2018* [2] *Ghandi et al. ASH 2018* [3] *Pick et al. Eur J Haematol. 2018* [4] *Chen et al. Blood 2018* [5] *Vogl et al. JCO 2018*

Selinexor Mechanism of Action



XPO1 in MM

- Transports >200 proteins from the nucleus to cytoplasm
- Expression increased in MM vs normal PC/MGUS/SMM
- Correlates with shorter survival and increased bone disease

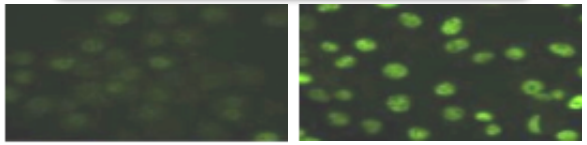
Selinexor

- Inhibits XPO1 through reversible covalent modification

Selinexor Mechanisms of Action

1. Nuclear retention/activation of **tumor suppressor proteins** and **glucocorticoid receptor**
2. Reduction of oncoproteins through nuclear retention of their **mRNAs**

p53 Localization



Control | Selinexor-Treated

Tai et al *Leukemia* 2014.
Schmidt et al *Leukemia* 2013.

Pivotal STORM Part 2: Study Design

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

Selinexor / dexamethasone twice weekly (Days 1 and 3) – 28 day cycle

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, a 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%; platelets >50,000/mm^3)
- Hemoglobin ≥8.5 g/dL

MM=Multiple Myeloma; IMiD=Imunomodulatory Drug; ANC=Absolute Neutrophil Count.

Patient Characteristics

	N=123*
Age: Years median (range)	65 (40–86)
Time from Diagnosis: Years median (range)	6.6 (1.1–23.4)
Males : Females	71 M (58%) : 52 F (42%)
Creatinine Clearance: <60 mL/min **<40 mL/min**	40 (33%) 15 (12%)
High Risk Cytogenetics: (del17p, t(4;14), t(14;16), 1q21)	65 (53%)
MM Subtype: FLC	35 (28%)
Revised International Staging System (R-ISS): I / II / III / Unk	16% / 64% / 19% / <1%
ECOG Performance Status: 0 / 1 / 2 / Unk	29% / 59% / 9% / 3%
Median % Change in MM Markers Between Screening to C1D1: (median 12 days)	22%

N=Number; M=Males; F=Females, MM=Multiple Myeloma; FLC=Free Light Chain.
*A total of 123 patients were enrolled, however 1 patient did not meet eligibility criteria (no exposure to carfilzomib), thus was excluded from efficacy analysis, however this patient was included in the safety analysis population.

Prior Therapies

	N=122*
Median Prior Regimens (range)	**7 (3–18)**
Number of Prior Treatment Regimens	
≤6	50 (41%)
7–8	36 (29.5%)
≥9	36 (29.5%)
Prior Treatments	
• Refractory to PI, IMiD, daratumumab, and a glucocorticoid	122 (100%)
• Refractory to carfilzomib, pomalidomide, and daratumumab	117 (96%)
• Refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and 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%)

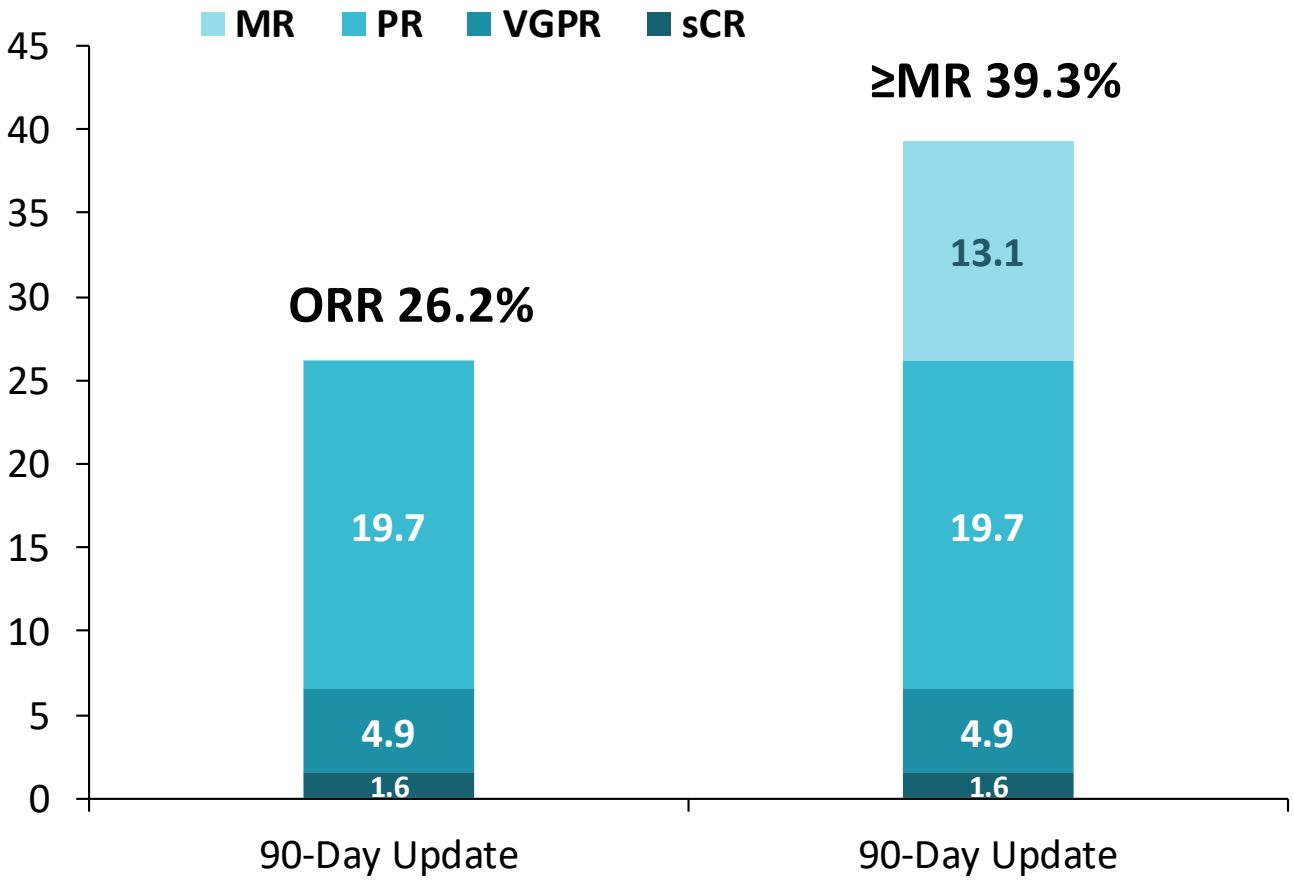
PI=Proteasome Inhibitors; IMiD=Immunomodulatory Drugs; CAR=Chimeric Antigen Receptor; N=Number.
*A total of 123 patients were enrolled, however 1 patient did not meet eligibility criteria (no exposure to carfilzomib), thus was excluded from baseline prior therapy analysis.

Patient Disposition

Total Treated Patients N=123	
On Treatment N=5 (4.1%)	
Discontinued Treatment N=118 (95.9%)	
Reasons for Discontinuation	
Disease Progression	65 (55.1%)
Adverse Event	38 (32.2%)
Related[a] to selinexor + dexamethasone	23 (19.5%)
Unrelated[a] to selinexor + dexamethasone	15 (12.7%)
Patient Withdrawal[b]	7 (5.9%)
Investigator Decision	4 (3.4%)
Other	4 (3.4%)

a. As determined by investigator.
b. Includes 3 patients lot to follow-up.
Data cutoff 17-AUG-2018; executed on 27-SEPT-2018

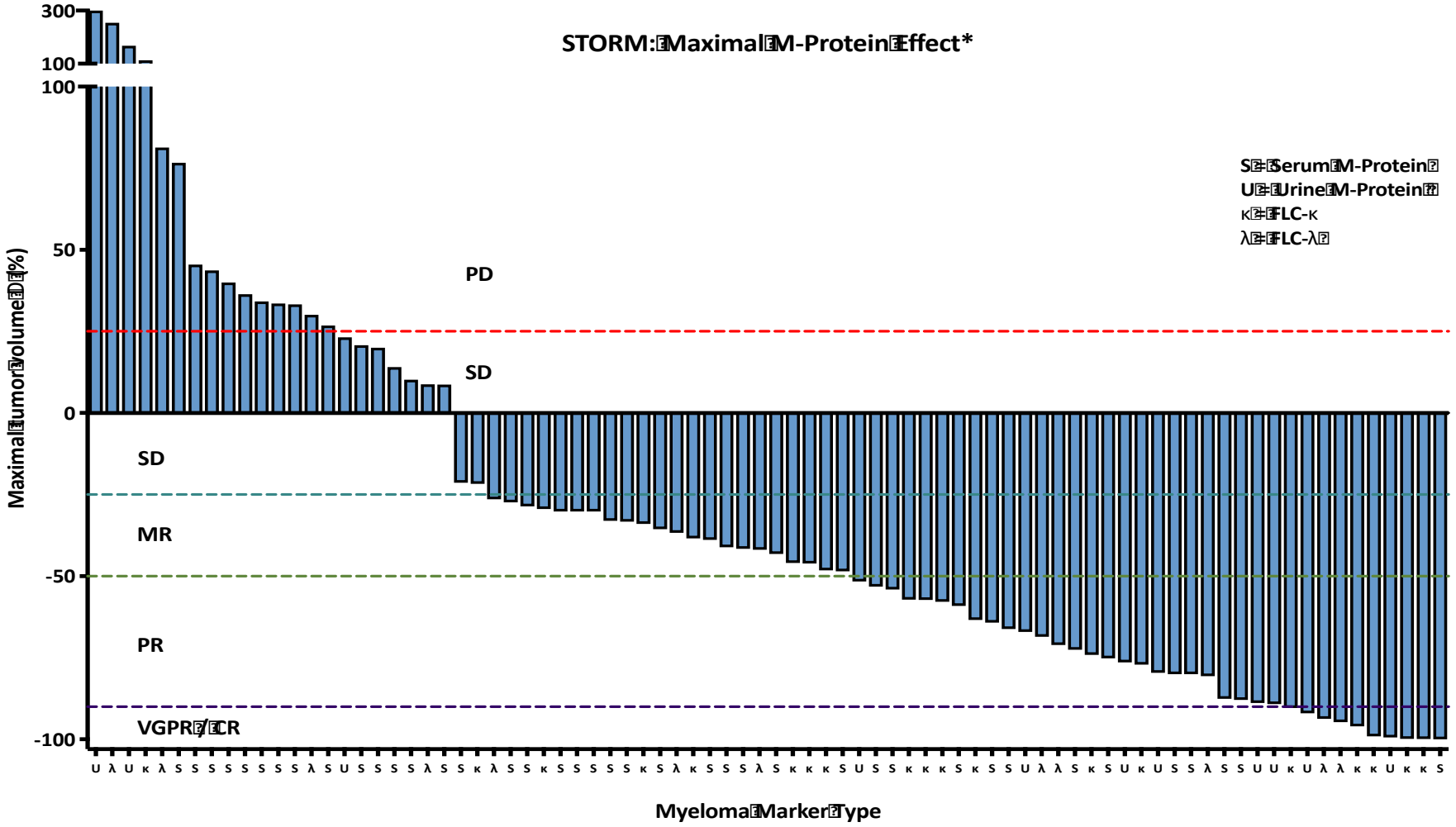
Efficacy



- Median of 7 prior treatment regimens, **ORR of 26.2%,** including **2 stringent CRs**
  - **sCRs MRD negative** at 10^{-6} and 10^{-4}
- Two patients with prior progression after CAR-T achieved a PR
- Median time to response was 1 month (range 1-14 weeks)
- Median duration of response was 4.4 months

sCR = Stringent Complete Response; VGPR = Very Good Partial Response; PR = Partial Response; MR= minimal response; MRD= Minimal Residual Disease, ORR = Overall Response Rate.
Responses as of August 17, 2018 were adjudicated according to the IMWG criteria *(Kumar, 2016)* by an independent review committee (IRC).

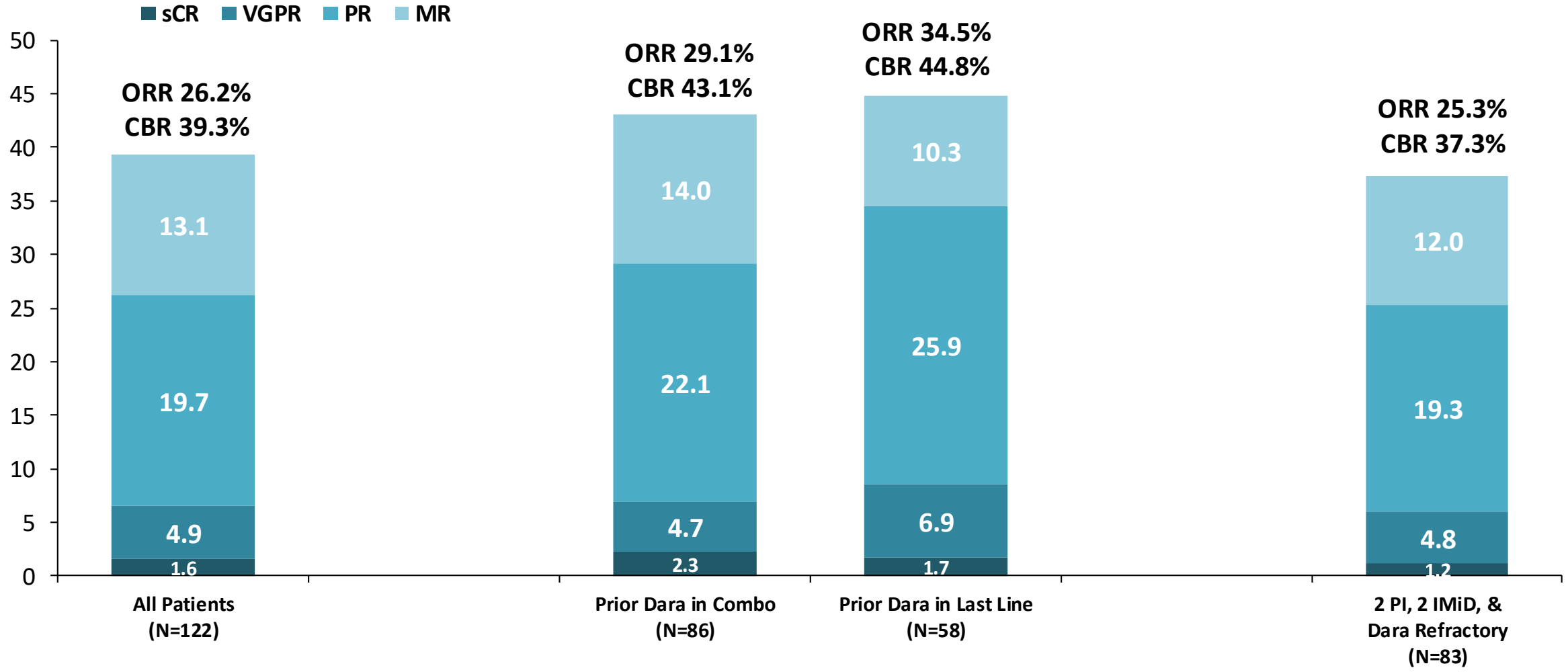
M-Protein Effect



- The majority of evaluable patients (71%) had reductions in M-protein
- ≥SD: 78.7%

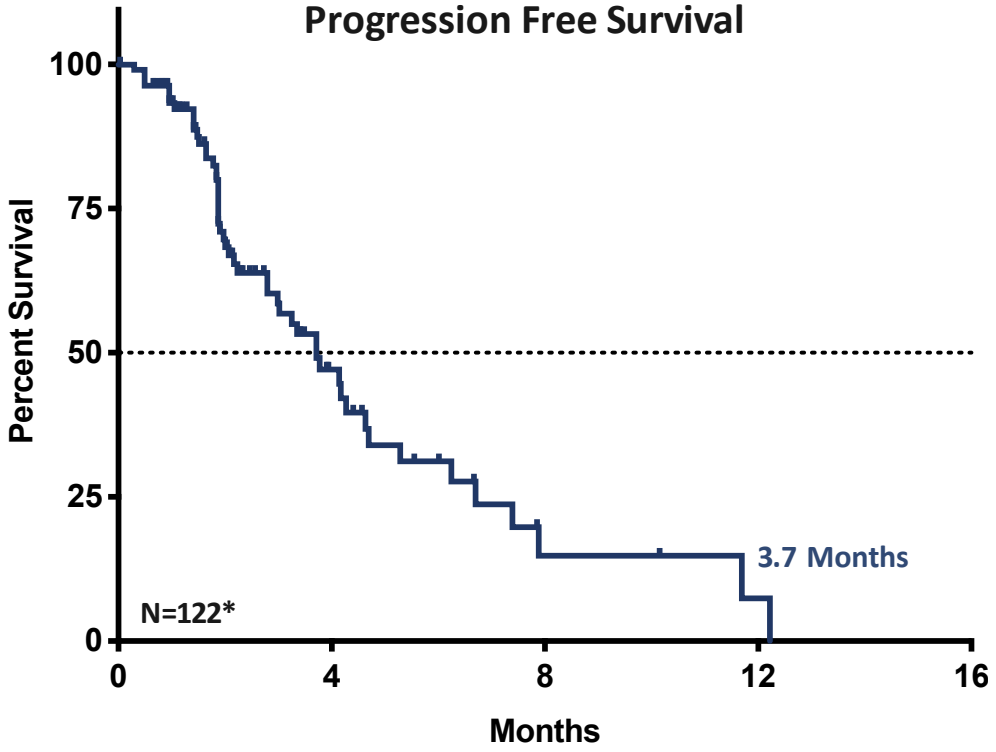
*M-protein changes shown for all patients with increases, and for patients with decreases ≤20% (30 patients with decreases 0 –19% not shown).

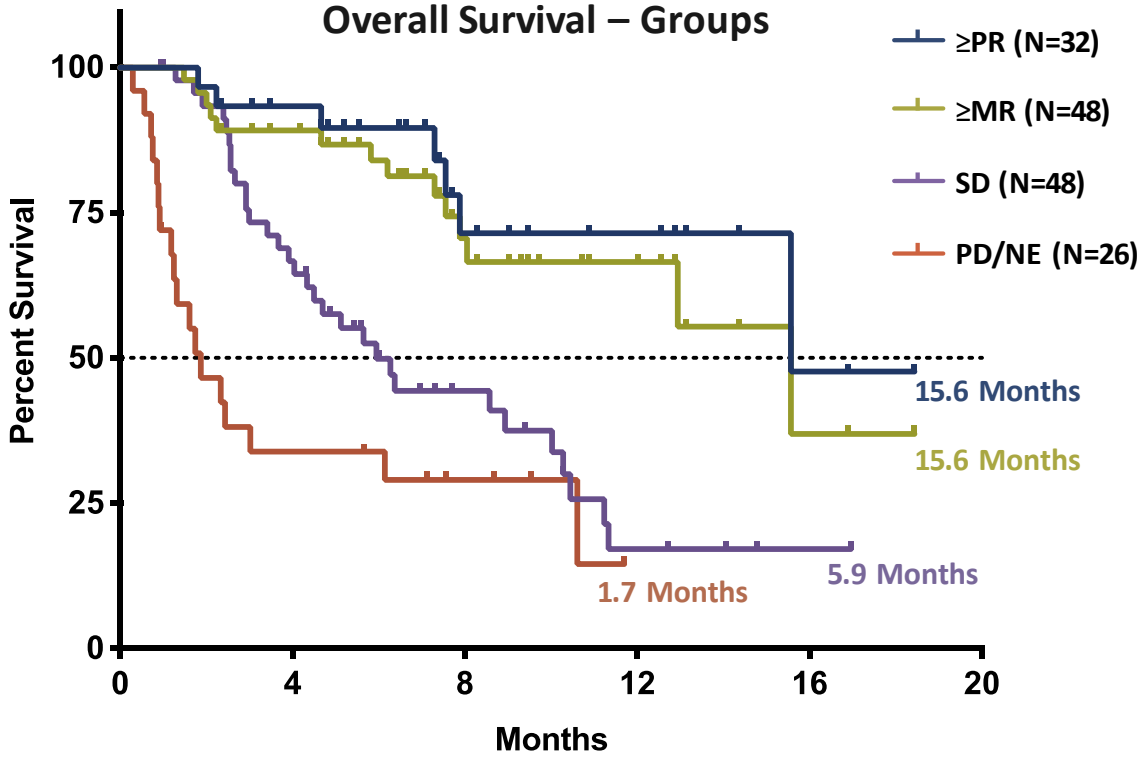
Efficacy Subgroups



MR=Minimal Response; PR=Partial Response; VGPR=Very Good Partial Response; sCR=Stringent Complete Response; ASCT=Autologous Stem Cell Transplant, N=Number; PI=Proteasome Inhibitor; IMiD=Immunomodulatory Drugs.

Progression Free and Overall 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	2.8 Months	1.1 Months
Median OS	8.6 Months	15.6 Months	15.6 Months	5.9 Months	1.7 Months

N=Number; PFS=Progression Free Survival; PR=Partial Response; MR=Minimal Response; SD=Stable Disease; PD=Progressive DiseaseNE=Non-evaluable; OS=Overall Survival.
*Not evaluable patients were censored on Day 1 for PFS (n=10) per statistical analysis plan

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

Gastrointestinal Disorders	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=123)
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	11 (8.9%)	35 (28.5%)	23 (18.7%)	--	**69 (56.1%)**
Asthenia	5 (4.1%)	6 (4.9%)	6 (4.9%)		**17 (13.8%)**
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%)	4 (3.3%)	--	**7 (5.7%)**
Sepsis[2]	--	--	--	1 (0.8%)	**2 (1.6%)**

[1]Pneumonia – 1 Grade 5 Event; note 14 (11.4%) treatment-emergent
[2]Sepsis – 1 Grade 5 Event; note 11 (8.9%) treatment-emergent
Data cutoff 17-AUG-2018; executed on 27-SEPT-2018

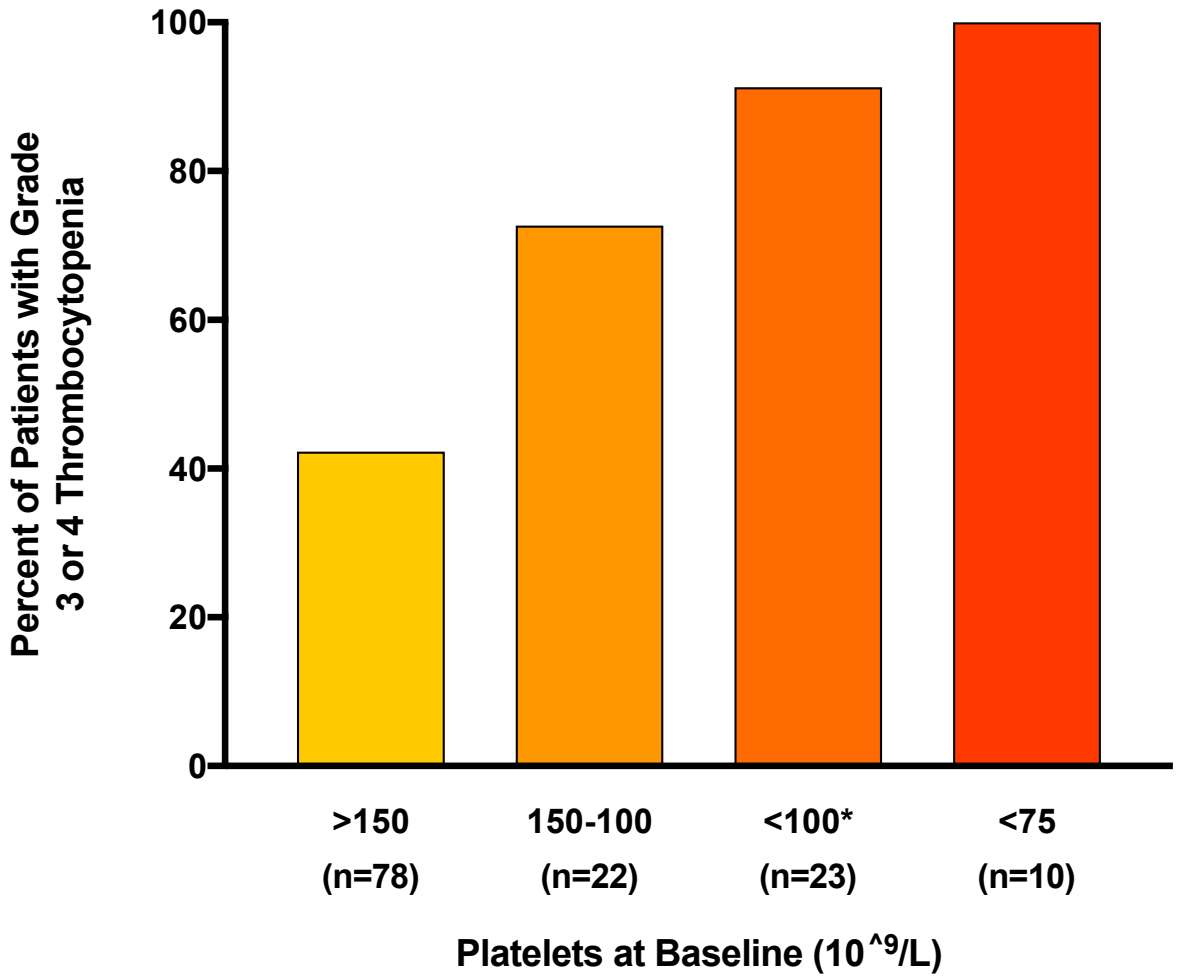
Treatment-Related Hematological Adverse Events in ≥10% of Patients

Adverse Event Term	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=123)*
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%)	19 (15.4%)	4 (3.3%)	**45 (36.6%)**
Leukopenia	6 (4.9%)	14 (11.4%)	16 (13.0%)	--	**36 (29.3%)**
Lymphopenia	2 (1.6%)	4 (3.3%)	8 (6.5%)	3 (2.4%)	**17 (13.8%)**

- 2 (1.6%) febrile neutropenia (Grade 3)

*23 patients discontinued therapy due to treatment-related AEs
Safety data cutoff 17-AUG-2018; executed on 27-SEPT-2018

Relationship of Thrombocytopenia to Baseline Platelet Count



* Includes patients in the <75 (10^9/L) group.

Side Effect Management

- In heavily pre-treated RRMM, the side effects of selinexor are dose and schedule dependent, and dose interruptions and reductions can lead to symptom improvement
- Median duration of selinexor + dexamethasone treatment was 9 weeks (range: 1-60+)
  - 98 (79.7%) patients required a dose modification
  - Among patients with a selinexor dose reduction, median duration of treatment was 13.5 weeks (range: 3-60+)
  - Majority of dose reductions occurred in the first two cycles
- Side effects were reversible, without evidence of major organ toxicities nor cumulative toxicity
- Essential to AE management: early identification, frequent assessment, and implementation of supportive care measures as needed, including:
  - Gastrointestinal: ondansetron, olanzapine, substance P/neurokinin antagonists
  - Hyponatremia: oral/IV hydration, salt tablets
  - Fatigue: methylphenidate
  - Thrombocytopenia: romiplostim or eltrombopag when selinexor is held

AE=adverse event; RRMM=Relapsed Refractory Multiple Myeloma.

Conclusions

STORM Part 2 represents the largest, most heavily-treated patient population with MM in a prospective clinical trial to date

- 122 patients with penta-exposed and triple class refractory MM
- Median 7 prior therapies over 6.6 years
- No available therapies with known clinical benefit - expected median overall survival (OS) ~1.7 months
- Patients had highly refractory MM - documented refractory to P, K, and D in 96% of patients

Due to aggressiveness of the disease, STORM treatment begins with high doses of selinexor in an effort to obtain rapid disease control

Most frequent Grade ≥3 AEs included hematologic, GI, constitutional, and low sodium

- AEs are generally reversible and manageable with dose modification and standard supportive care agents

GI=gastrointestinal.

Conclusions (continued)

Selinexor plus dexamethasone achieved:

- Overall response rate of **26.2%** in penta-exposed and triple class refractory MM
  - 2 patients achieved sCRs: both MRD negative
  - Two patients with prior progression after CAR-T achieved a PR
- Duration of response **4.4 months**
- ≥MR: 39.3%; ≥SD: 78.7%
- Median overall survival: **8.6 months**; 15.6 months in patients that achieved ≥MR versus 1.7 months in patients with PD/NE

Selinexor is the first investigational oral therapy to show activity in very heavily pretreated penta-exposed and triple class refractory MM

Biomarkers of selinexor resistance[1] and combination studies with MM backbone agents are ongoing

sCR=Stringent Complete Response; MRD=Minimal Residual Disease; PR=Partial Response; CAR-T=Chimeric Antigen Receptor T-Cell Therapy; SD=Stable Disease; OS=Overall Survival; MR=Minimal Response; PD=Progressive Disease; NE=Non-evaluable

1 Lagana et al ASH 2018 Poster 3216.

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