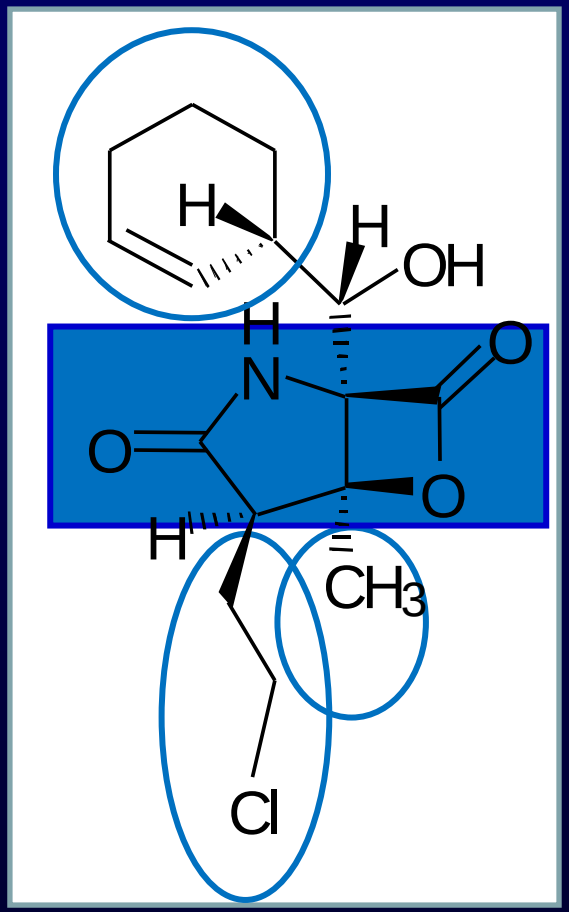
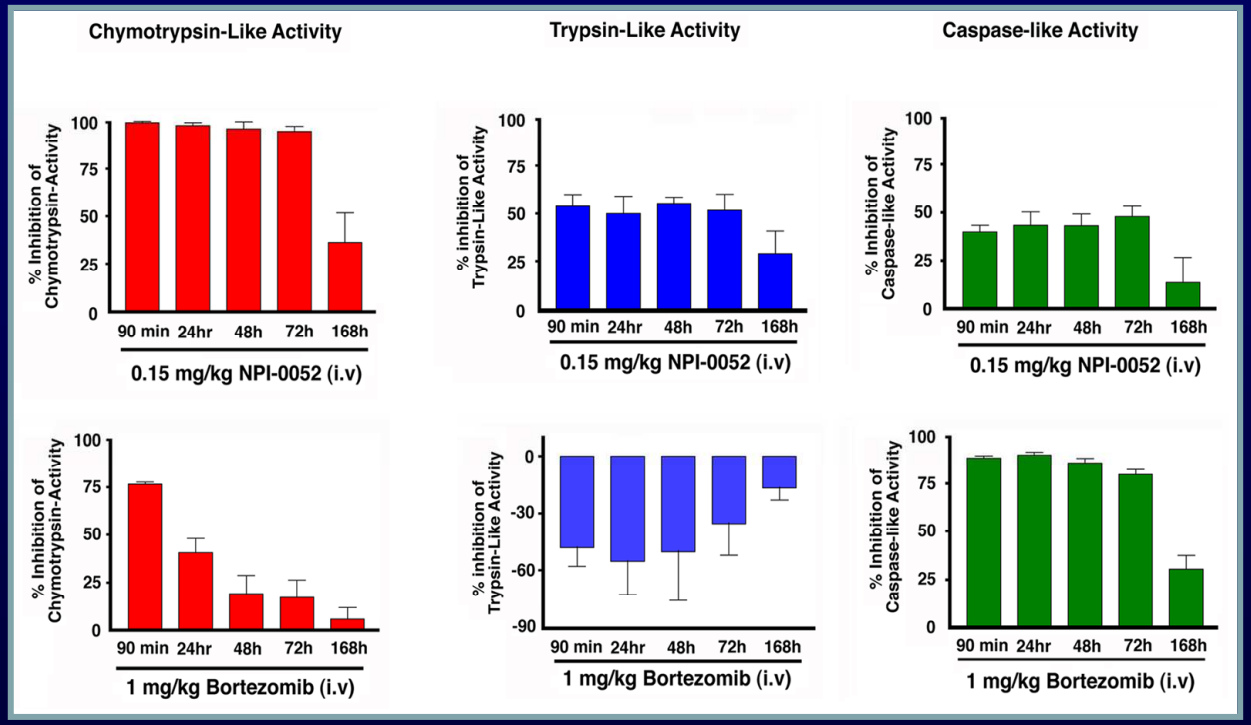
Phase 1 Clinical Evaluation of Twice-Weekly Marizomib (NPI-0052), a Novel Proteasome Inhibitor, in Patients with Relapsed/Refractory Multiple Myeloma (MM)

Paul Richardson MD, Andrew Spencer MD, Paul Cannell MD, Simon J. Harrison MD PhD, Laurence Catley MD, Craig Underhill MD, Todd M. Zimmerman MD, Craig Hofmeister MD, Andrzej Jakubowiak MD PhD, Jacob Laubach MD, Jonathan Kaufman MD, Michael A. Palladino PhD, Angie M. Longenecker RN, Ana Lay, Saskia Neuteboom PhD, Sandra Wear RN, G. Kenneth Lloyd PhD, Alison L. Hannah MD, Steven D. Reich MD, Matthew A. Spear MD, Kenneth C. Anderson MD

Marizomib: A Non-Peptide Proteasome Inhibitor Induces Rapid, Broad and Prolonged Inhibition

Marizomib (NPI-0052)

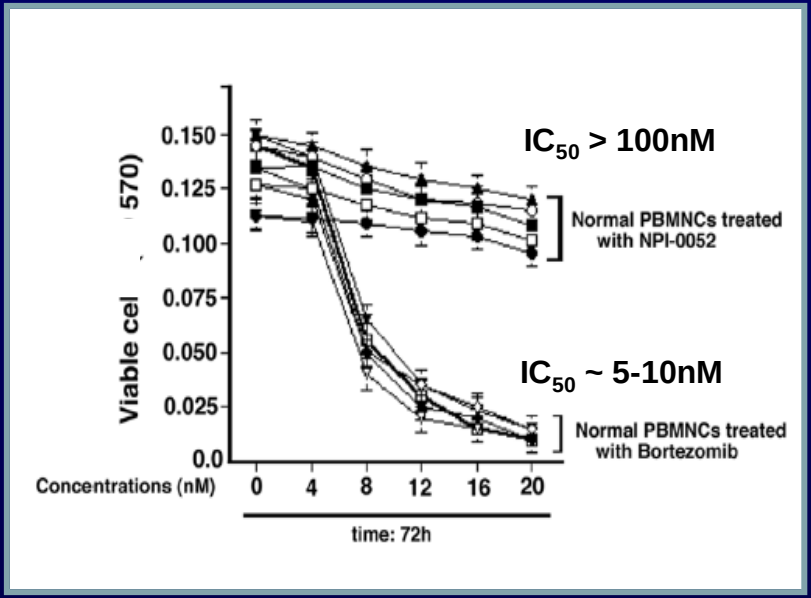




- Exhibits high levels of proteasome inhibition without toxicities associated with bortezomib
- Active in bortezomib and IMiD resistant myeloma preclinically

Chauhan et al., Cancer Cell, 8, 407-419, 2005

Marizomib has a High Therapeutic Index (TI) Preclinically and Safe Profile on Normal Cell Types

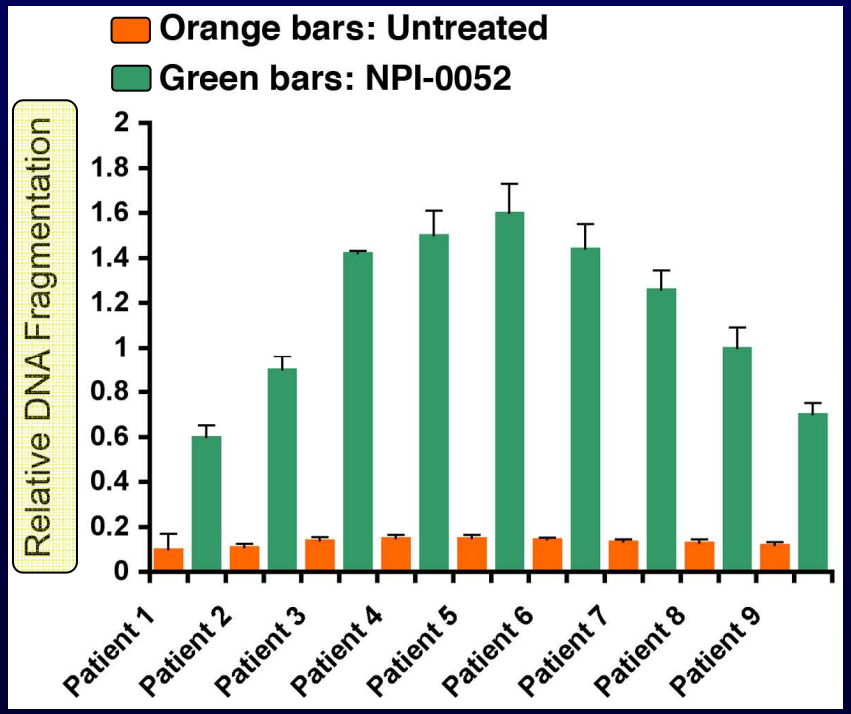


Human Cell Type	IC_{50} (nM)	
	Marizomib	Bortezomib
RPMI 8226 (multiple myeloma)	9.1 ± 0.8	5.7 ± 1.3
CCD-27sk (normal fibroblasts)	510 ± 160	15 ± 2.7
Ratio CCD:RPMI	56	2.6

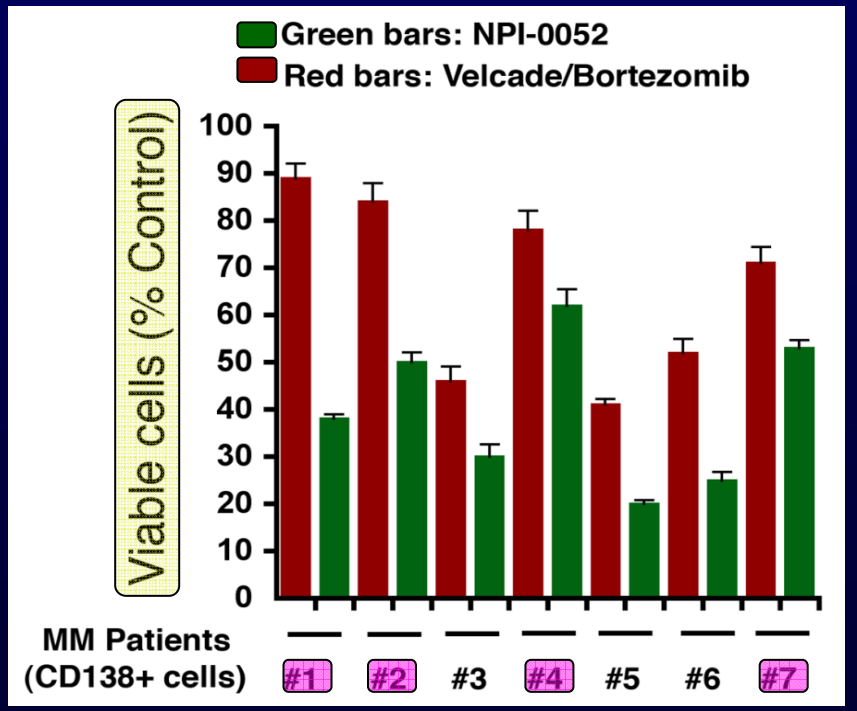
- Minimal inhibition of PBMC viability after 72h of treatment with marizomib compared to bortezomib
  - Chauhan et al., Cancer Cell, 2005
- Greater TI versus bortezomib on viability of normal human fibroblasts and MM cells
  - Chauhan et al., Cancer Cell, 2005
- No observed toxicity in human CFU assays for CFU-E, BFU-E, CFU-GM and CFU-GEMM
  - Baritaki et al., J. Immunology, 2008
- Minimal effect on normal human neural stem cell viability compared to malignant glioma cells
  - Safai et al., submitted 2011

Marizomib is Active in Dexamethasone, Thalidomide and Bortezomib Refractory Multiple Myeloma (MM) in Preclinical Models

MM cells from patients refractory to dexamethasone and thalidomide

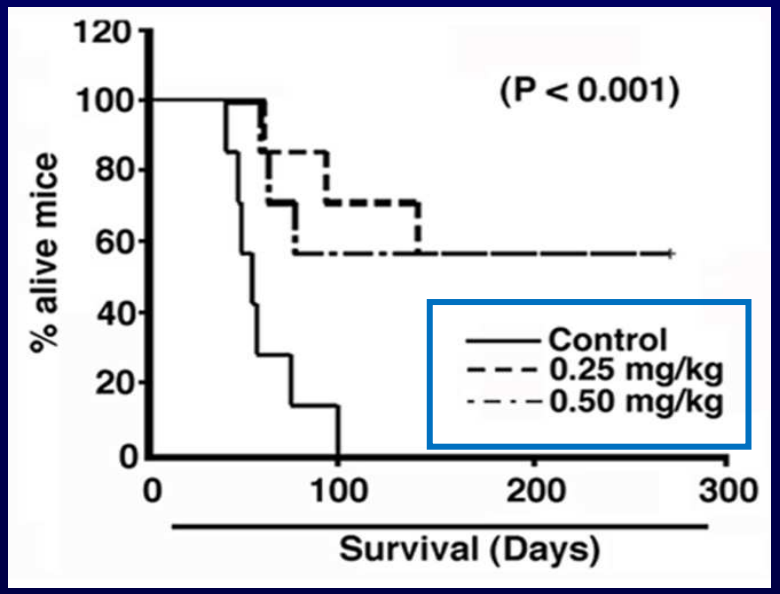


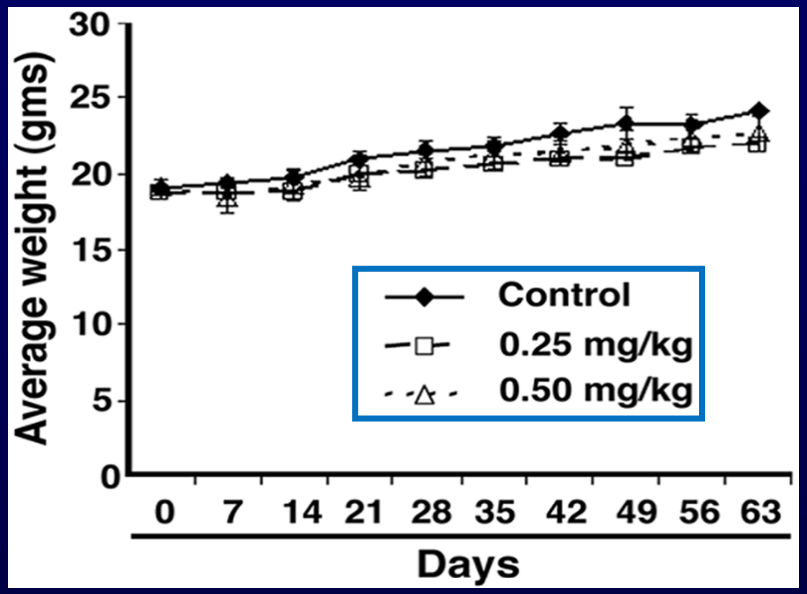
MM cells from patients also refractory to bortezomib



Chauhan et al., Cancer Cell 2005, 8(5):407-419

Marizomib Inhibits Growth of MM.1S Xenografts in an *In-Vivo* Model

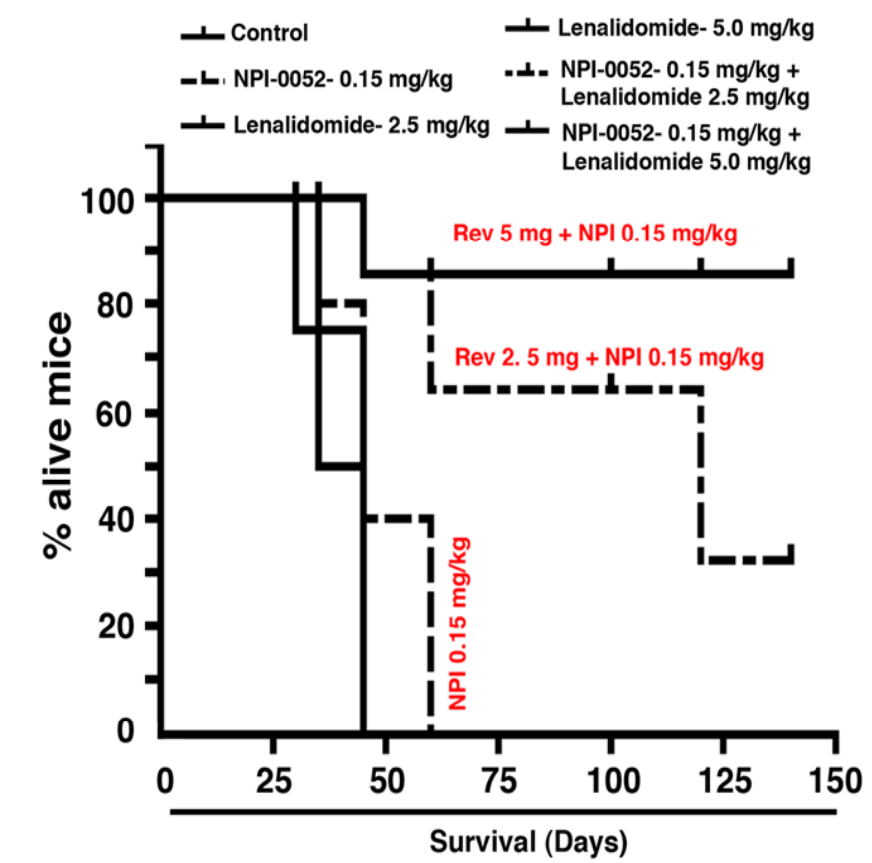




- Marizomib was administered orally twice-weekly for 13 weeks.
- Marizomib is well tolerated and prolongs survival with significantly reduced tumor recurrence.
- Similar reduced tumor recurrence is obtained with marizomib administered IV at 0.15 mg/kg.

Chauhan et al., Cancer Cell 2005, 8(5):407-419

Marked Synergistic Activity and Safe Profile for Marizomib and Lenalidomide Combinations in MM Models



Mechanisms of action for lenalidomide in MM

- Inhibits angiogenesis
- Alters production of multiple cytokines
- Activates T-cells, NK-cells and enhances ADCC
- Inhibits NF-kB activity
- Reduces MM cell adhesion to BM stromal cells
- Activates caspase 8
- Downregulates apoptosis inhibitors, cIAP2 and Flice-inhibitory protein

Mechanisms of action for the combination in MM

- Triggers Endoplasmic Reticulum stress
- Upregulates 3 isoforms of the proapoptotic BIM
- siRNA BIM inhibited apoptosis of combination
- Enhances marizomib inhibition of 20 S proteasome proteolytic activities

Chauhan et al, Blood 2010; 115: 834-845

Phase 1 Clinical Trials with Marizomib to date

- Four different studies
- US, Australia and Estonia
- Multiple tumor types
  - Multiple Myeloma (MM)
  - Lymphomas
  - Leukemias
  - Solid tumors
- Multiple dosing regimens:
  - Weekly for 3 doses in 28 day cycles
    - IV infusions of 1 and 10 minutes
  - Twice weekly for 4 doses in 21 day cycles
    - IV infusions of 1, 10, 60 and 120 minutes

Study Designs in MM with Marizomib (MZ) IV (NPI-0052-101 & NPI-0052-102)

- **Dosing Regimens**:

Weekly x 3 doses, 28 day cycles, infusions of 1 and 10 min

Twice weekly x 4 doses, 21 day cycles, infusions of 1, 10, 60 and 120 min

- Dexamethasone
  - NPI-0052-101: If no response by end of Cycle 2, 20 mg day of and day after marizomib dose.
  - NPI-0052-102: 20 mg administered day before and day of marizomib dose.

- Escalation: Accelerated Dose Titration
  - Dose escalation in 100% increments, until drug related ≥ Grade 2 toxicity or 0.3 mg/m^2, thereafter dose increases of up to 50% increments.
  - Cohorts ≥ 1-3 pts, with expansion to 6 in the event of DLT.
  - Recommended Phase 2 Dose (RP2D) cohorts of up to 24 pts.

Key Eligibility Criteria:

- **Inclusion:**
  - MM for which no other approved treatment is available and clinically indicated (for NPI-0052-101 relapsed or relapsed/refractory required).
  - Karnofsky Performance Status (KPS) ≥ 70%
  - Labs (NPI-0052-101 and NPI-0052-102)
    - Hemoglobin ≥ 8-9 g/dL
    - Absolute Neutrophil Count ≥ 1.0 x 10^9 /L
    - Platelet count ≥ 30-50 x 10^9 /L
    - Serum bilirubin ≤ 1.5 x ULN
    - AST ≤ 2.5 x ULN
    - Serum creatinine ≤ ULN (1.8 mg/dL in RP2D)
    - Creatinine clearance ≥ 50-60 mL/min
  - Signed informed consent

- **Exclusion**
  - Patients with > Grade 1 proteinuria: 1 g/24 hr excluding m-proteins (total urine protein minus paraprotein), untreated urinary tract infection, as well as any pre-existing kidney disease (acute or chronic) in the investigator's assessment would impose excessive risk to the patient.

Patient Demographics

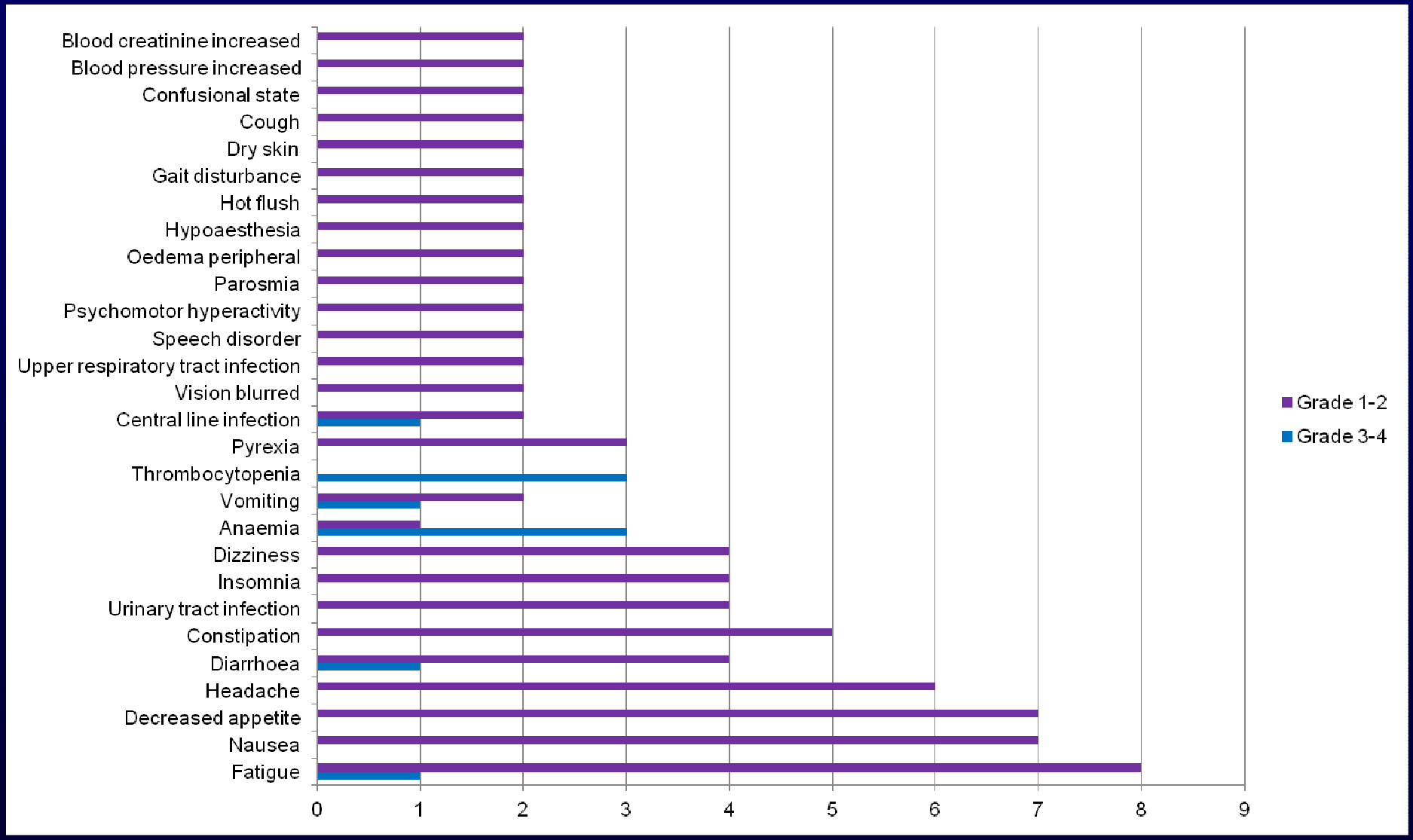
	NPI-0052-101	NPI-0052-102
Patients	44	25
Median age (years)	61	63
Male/Female	25 / 19	13 / 12
KPS 80 -100 70	40 4	23 2
Time from Initial Diagnosis (median years)	5.01 (1.42 – 14.38)	5.79 (1.76-13.41)
Number of Prior Regimens (median)	5 (1 – 11)	7 (2 – 13)
Prior Dexamethasone	44 (100%)	25 (100%)
Prior Bortezomib Prior Bortezomib Regimens (median) Refractory to Prior Bortezomib	32 (73%) 2 17/32 (53%)	17 (74%) 1 11/17 (65%)
Prior Immunomodulatory Drug Thalidomide Lenalidomide	40 (91%) 33 (75%) 29 (66%)	23 (100%) 21 (91%) 20 (87%)

Patient Disposition:

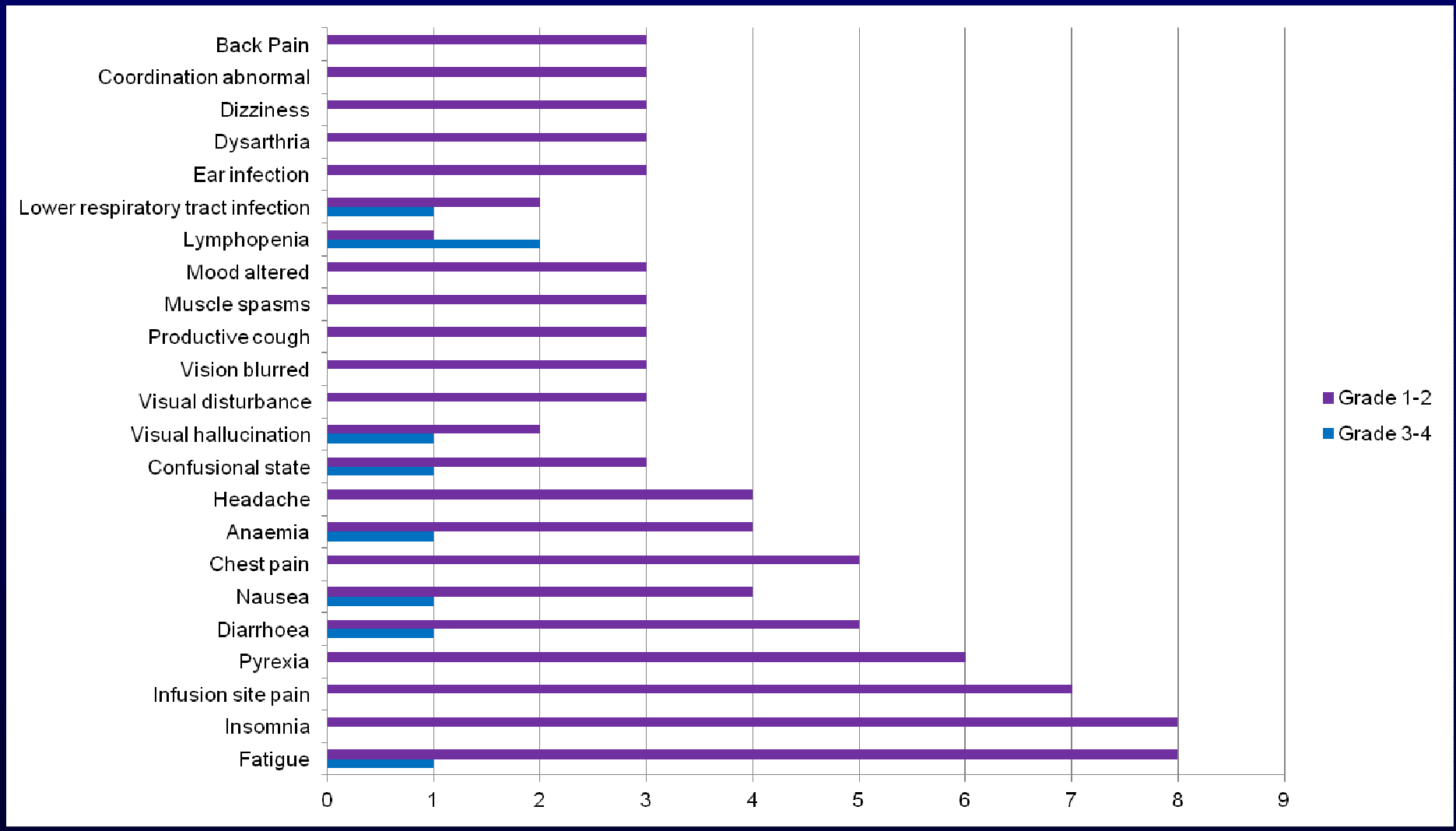
Pts Treated with Twice Weekly Infusions[a]			
NPI-0052-101		NPI-0052-102	
Cohort (mg/m^2)	Number of Patients	Cohort (mg/m^2)	Number of Patients
0.15	3	0.075[b]	2
0.4	4	0.075	3
0.6	2	0.15	2
0.5 (2 hr)	3	0.3	3
		0.4	3[c]
		0.5	6[d]
		0.6 (2 hr)	3
		0.5 (2 hr)	3
Total	12	Total	25

[a] Infusions were 1, 10, or 60 mins unless denoted as 2 hr
[b] Liquid formulation: all others were lyophile formulation
[c] DLT of intermittent expressive aphasia
[d] DLT of elevated liver function tests

Marizomib Twice Weekly (NPI-0052-101) Adverse Events in >10% of Patients (n=12)

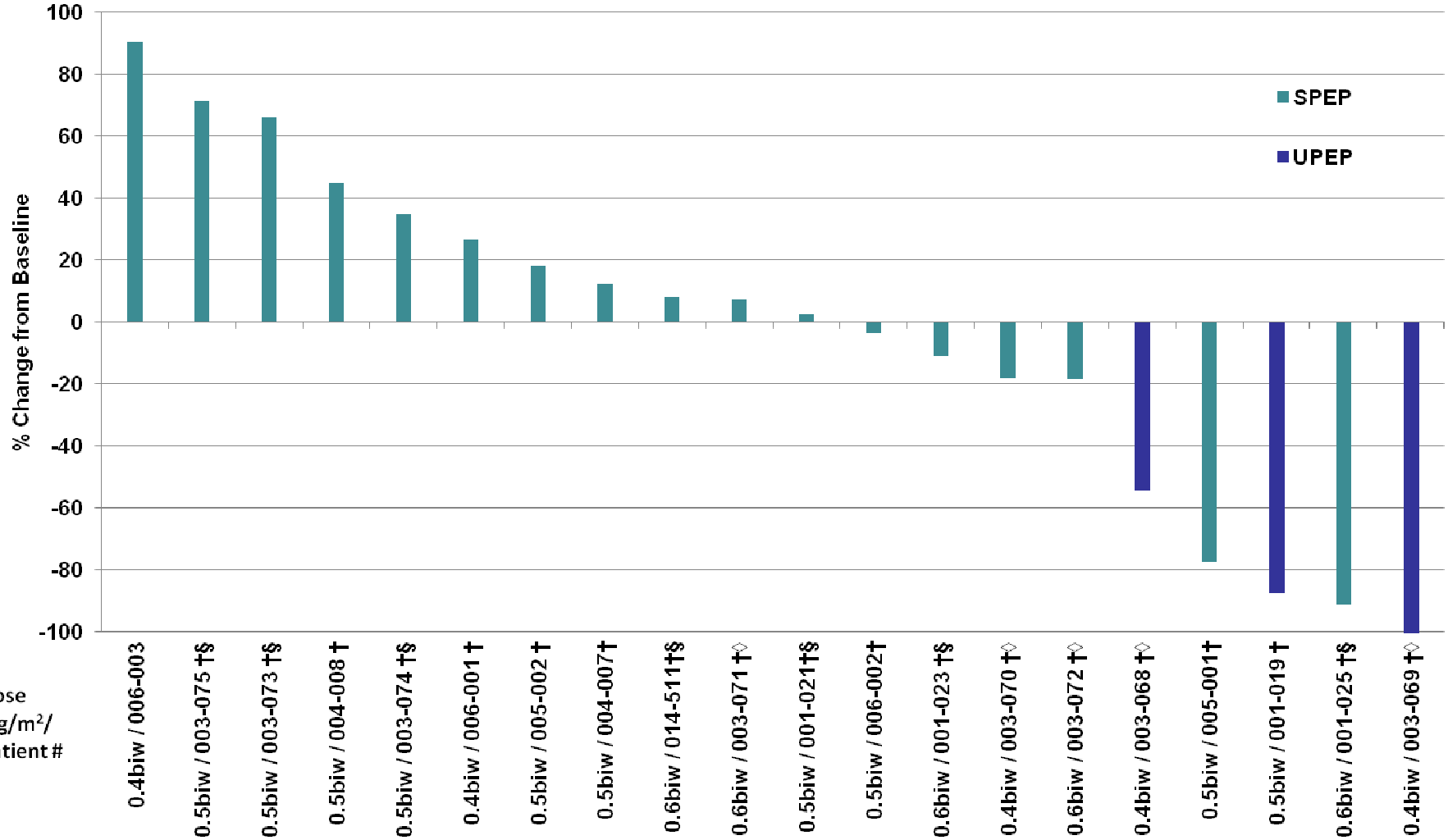


Marizomib Twice Weekly (NPI-0052-102) Adverse Events in >10% of Patients (n=24*)



*** Complete data not available for one patient.**

Best Paraprotein Response (as measured by M Protein): NPI-0052 0.4-0.6 mg/m^2 BIW (n=20)



† Received prior bortezomib ◊ 1 hour infusion biw § Two hour infusion biw

Responses to Marizomib +/- Dexamethasone in Evaluable Pts at Full Dose [≥0.4 mg/m²]* Twice Weekly (n=21**)

All Pts		
EBMT		
≥ SD	11/20	55%
MR + PR	3/20	15%
Uniform Criteria		
≥ SD	12/21	57%
PR + VGPR	4/21	19%

Pts Refractory to Bortezomib		
EBMT		
≥ SD	8/12	67%
MR + PR	2/12	17%
Uniform Criteria		
≥ SD	8/12	67%
PR + VGPR	2/12	17%

Median Duration of Response (all Pts) = 133 days (~ 5 mos)

Pts Exposed to Bortezomib		
EBMT		
≥ SD	11/19	58%
MR + PR	3/19	16%
Uniform Criteria		
≥ SD	11/19	58%
PR + VGPR	3/19	16%

Pts Refractory to Lenalidomide		
EBMT		
≥ SD	8/13	62%
MR + PR	3/13	23%
Uniform Criteria		
≥ SD	9/14	64%
PR + VGPR	4/14	29%

- Response criteria defined with baseline SPEP ≥ 0.5 g/dL or UPEP ≥ 200 mg/24h with at least 2 assessments after treatment Day 1 for EBMT ; also by free lite for UC**.
- Refractory defined as having PD during or within 60 days of last regimen.

*As of 05 Dec 11

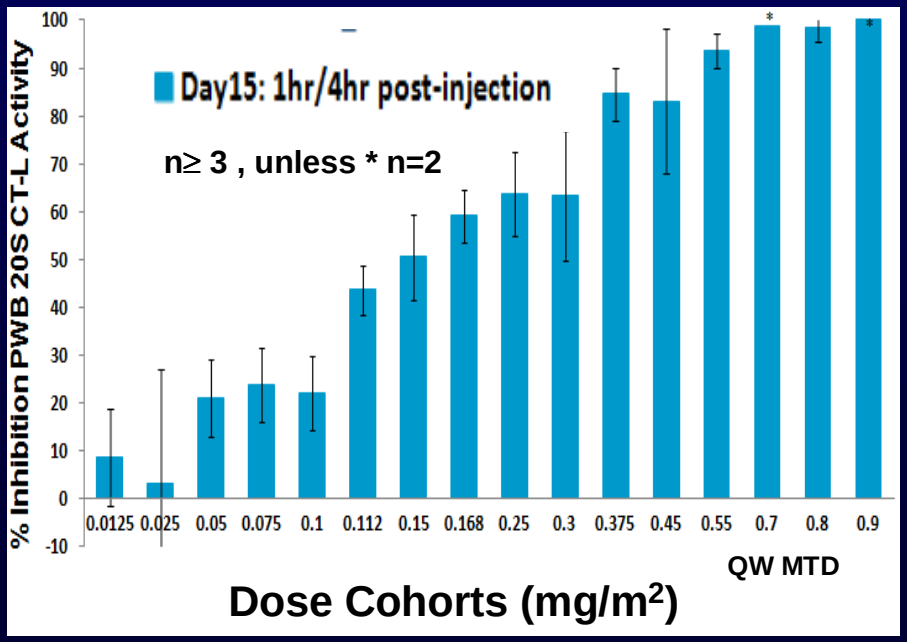
Pharmacokinetic/Pharmacodynamic Summary

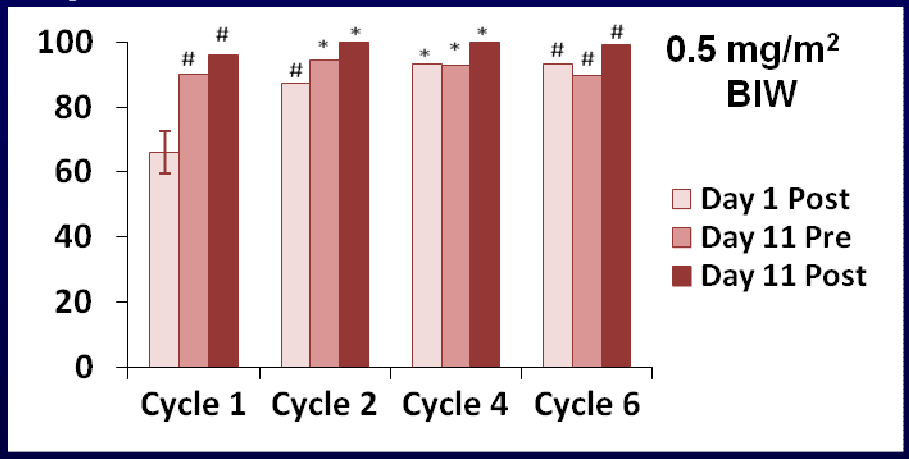
- Distributes rapidly to tissues (seconds to minutes)
- Short PK half-life, long PD duration, reduced potential for off-target effects
- No apparent accumulation: At RP2D: AUC_{total} D1 = 423.3; D15 = 415.8 ng/mL*min
- PWB 20S Proteasome Chymotrypsin-like (CT-L) activity

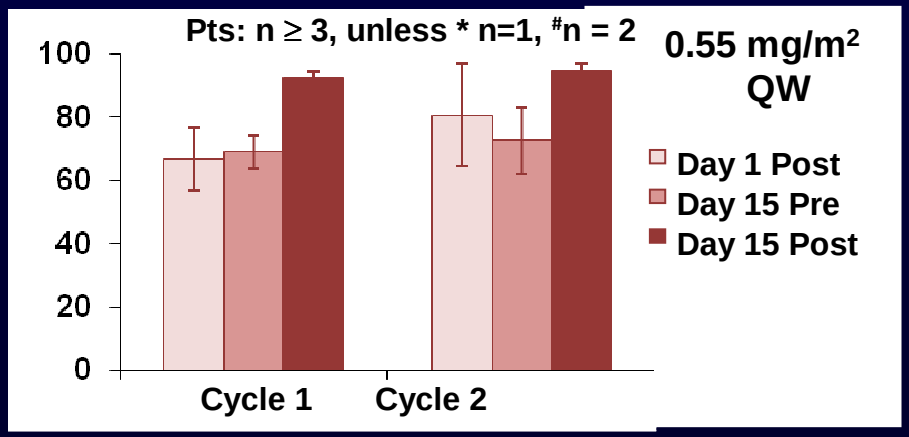
Combined data from NPI-0052-100, 101 and 102: QW Dosing

- BIW dosing results in faster, maximum proteasome CT-L inhibition

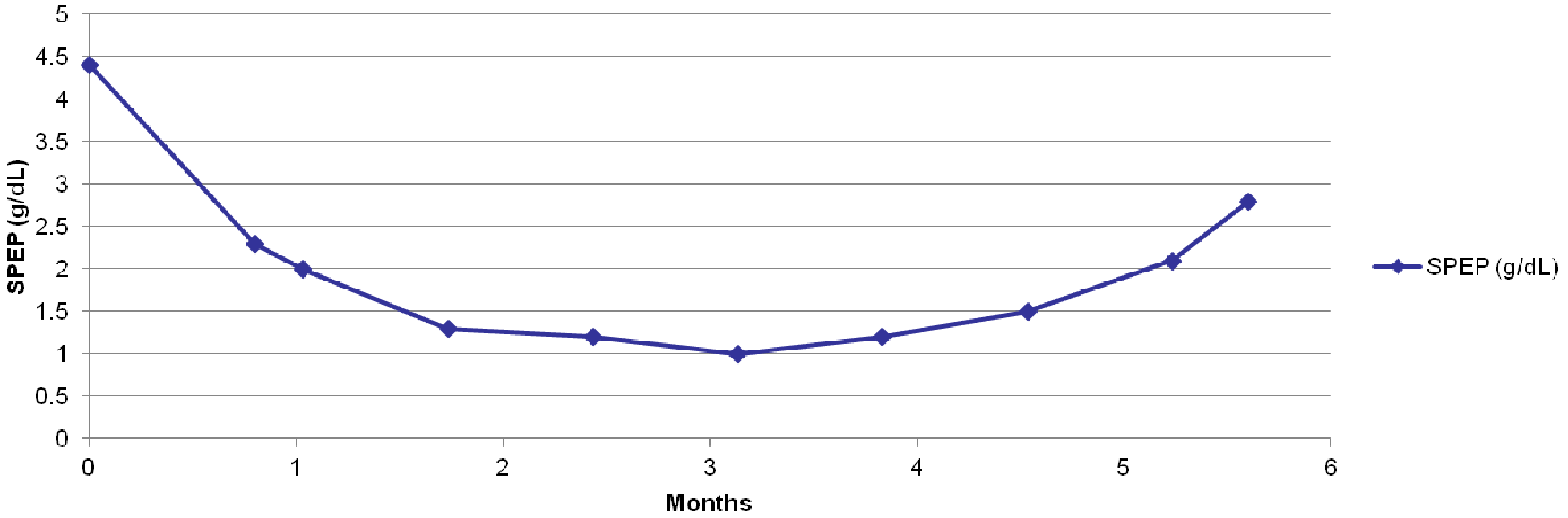
Palladino, et al. EORTC, 2008





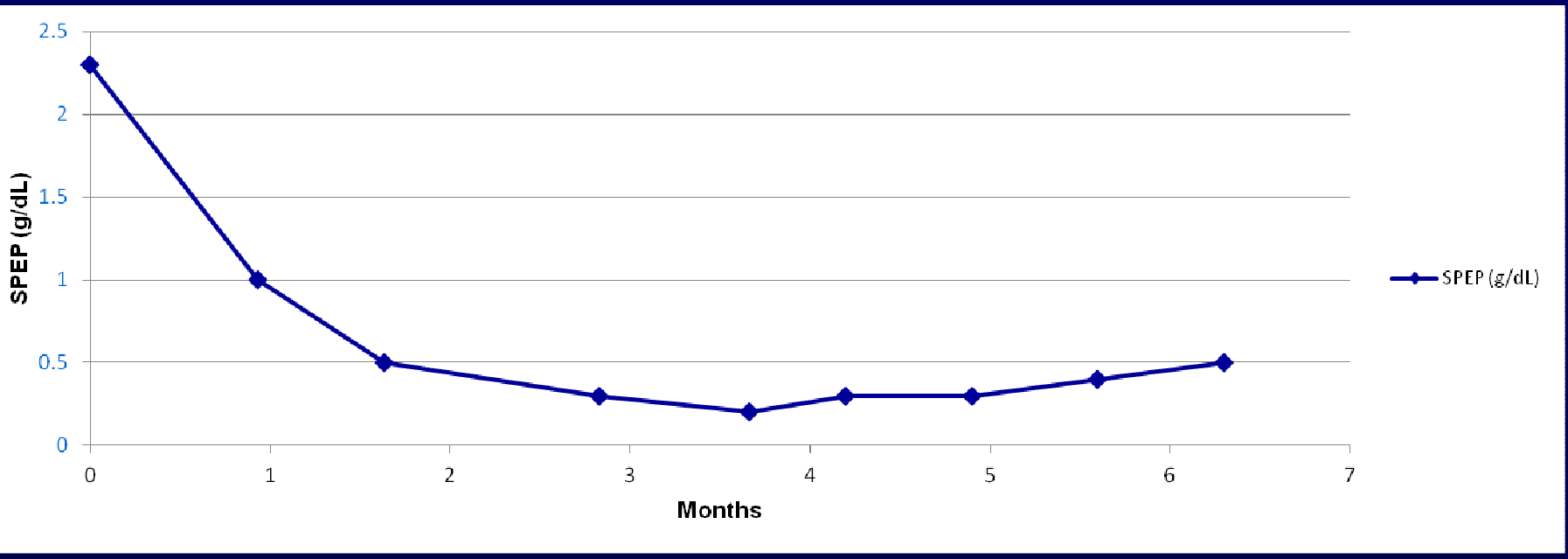


Patient 005-001 (NPI-0052-102)
Bortezomib Refractory / Lenalidomide Refractory



Prior Regimen	Start Date	Stop Date	Best Response to Treatment	Outcome
VINCRISTINE/ADRIAMYCIN/DEXAMETHASONE	21-Aug-03	24-Oct-03	PR	Proceeded with transplant
AUTOLOGOUS BONE MARROW TRANSPLANT	4-Feb-04	N/A	PR	Response with subsequent PD
THALIDOMIDE/PREDNISOLONE MAINTENANCE	23-Mar-04	22-Feb-05	PR	Subsequent PD
CYCLOPHOSPAMIDE/DEXAMETHASONE.	20-Sep-06	29-May-07	MR	Completed course of therapy
LENALIDOMIDE / DEXAMETHASONE	20-Jun-07	12-Feb-08	PR	Response with subsequent PD
BORTEZOMIB	22-Feb-08	22-May-08	PR	Proceeded with transplant
AUTOLOGOUS STEM CELL TRANSPLANT #2	10-Jul-08	N/A	PR	Response with subsequent PD
BORTEZOMIB	10-Mar-09	5-Oct-09	PR	Completed course of therapy
BORTEZOMIB / LENALIDOMIDE/ DEXAMETHASONE	28-Jan-10	1-Apr-10	PD	Primary resistance (no response to therapy)
RADIOTHERAPY TO LUMBAR SPINE	12-Mar-10	27-Mar-10	n/a	Completed course of therapy

Patient 001-025 (NPI-0052-102)
Bortezomib Refractory / Lenalidomide Refractory



Prior Regimen	Start Date	Stop Date	Best Response to Treatment	Outcome
CYCLOPHOSPHAMIDE + IDARUBICIN + DEXAMETHASONE	Apr-02	Jun-02	PR	Completed course of therapy
CYCLOPHOSPHAMIDE	Nov-02	Feb-03	MR	Proceeded with transplant
AUTOLOGOUS STEM CELL TRANSPLANT	26-Feb-03	26-Feb-03	PR	Partial Response
PREDNISOLONE MAINTENANCE	22-Apr-03	25-Nov-04	PR	Sustained Response then subsequent PD
DOXORUBICIN HCL + BORTEZOMIB	Aug-05	Dec-05	PD	No response and subsequent PD
LENALIDOMIDE AND DEXAMETHASONE	Apr-08	Oct-10	PR	Partial response with PD after 30 months
AKT INHIBITOR (GSK2110183)	10-Dec-10	24-Mar-11	PR	Transient response with subsequent PD

Summary/Future Directions

- Marizomib is generally well tolerated at effective doses:
  - Common AEs include fatigue, nausea, vomiting, headache, dizziness, and fever.
  - Dose limiting toxicities include transient hallucinations, reversible cognitive changes.
  - Peripheral neuropathy, thrombocytopenia and neutropenia were not seen.
- Pharmacodynamics: Proof-of-mechanism demonstrated.
- Pharmacokinetics: Short-half life, large volume of distribution.
- Twice weekly dosing with longer infusions is active with manageable toxicity.
- Twice weekly MTD and RP2D: 0.5 mg/m^2 (by 2 hr infusion).
- Further studies of marizomib in MM with monotherapy +/-dexamethasone and other combination approaches (eg, marizomib + lenalidomide + dexamethasone) are warranted.

Acknowledgements:

- Patients and their Families
- Investigators and their Research Teams
- Dana Farber – Dharminder Chauhan PhD, Nora Loughney, Deborah Doss RN, Maureen French, Diane Warren
- Chicago – Daniel Larsen, Monica Mitchell RN
- Michigan – Diane Durecki, Terri Jokbar RN, Jessica Lantz
- Ohio – Mindy Bowers
- Emory – Dixil Francis
- The Alfred – Anne Buckland
- Peter Macallum – Amanda Marshall
- Queen Elizabeth – Sue Yeend RN, Louise Pirc
- Mater Adult Hospital – Kathryn Lape RN
- Royal Perth – Megan Margaria
- Border Medical Oncology – Anne Harris
- MMRC – Susan Kelly MD
- Nereus – Natasha Reddinger