NPI-0052-101

Phase 1 Clinical Trial of the Novel Structure Proteasome Inhibitor NPI-0052 in Patients with Relapsed and Relapsed/Refractory Multiple Myeloma (MM)

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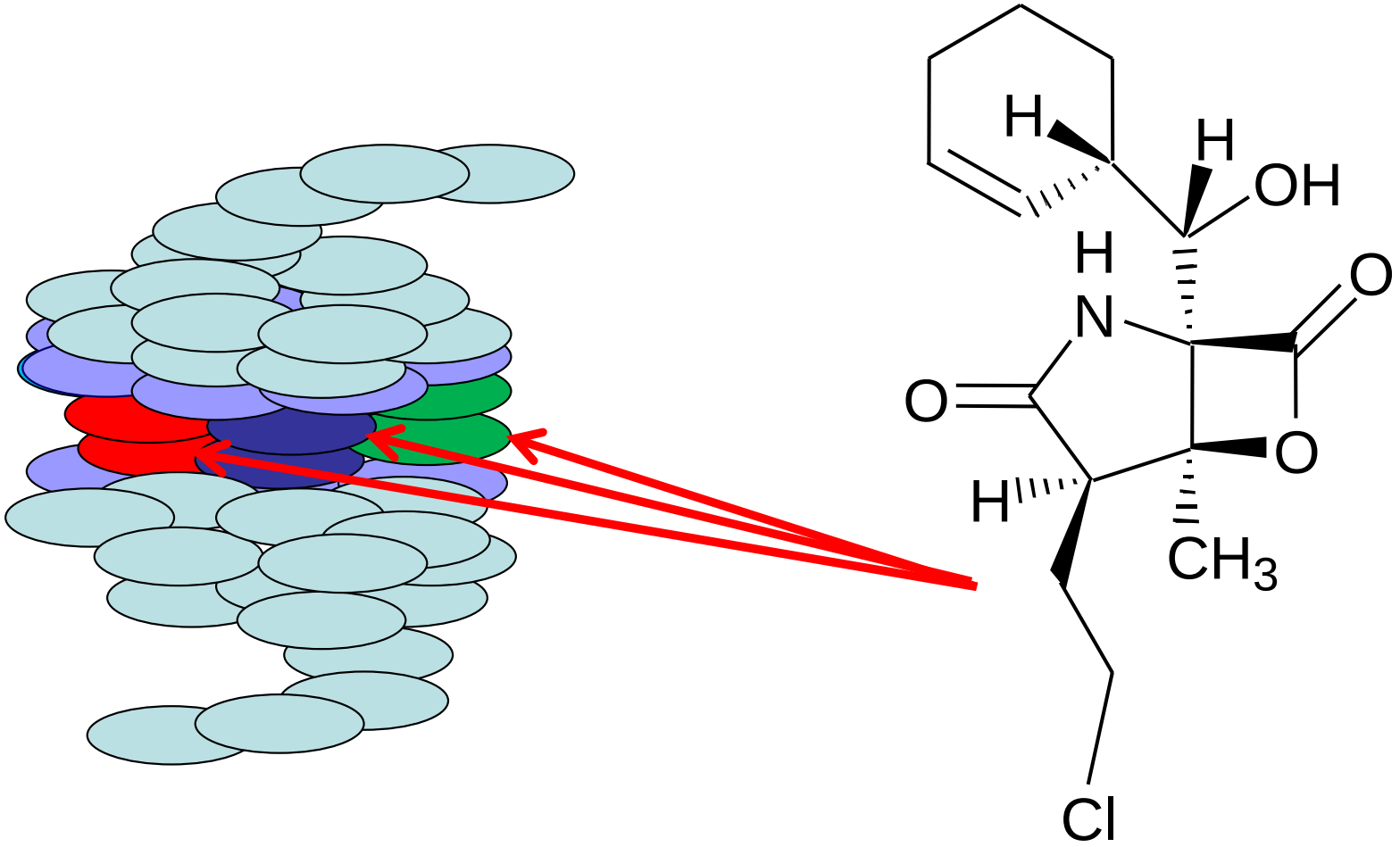
NPI-0052



BACKGROUND

NPI-0052

Novel second generation 20S proteasome inhibitor (non-peptide based)

Unique proteasome inhibition profile:

- **Fast, marked and prolonged inhibition of all 3 proteolytic activities**

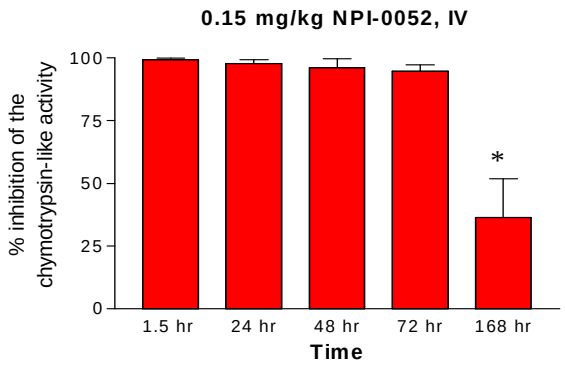
Unique toxicology profile:

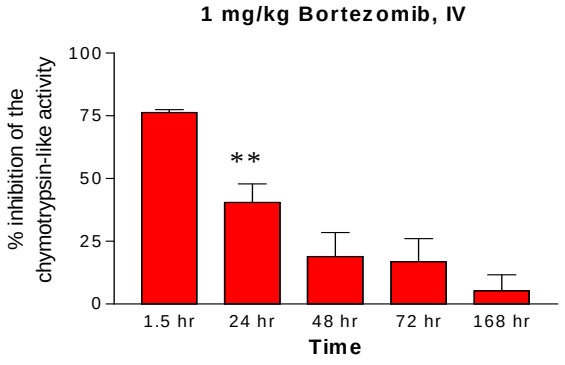
- **High levels of proteasome inhibition can be achieved**
- **Toxicities frequently reported with bortezomib do not appear to be elicited by NPI-0052 at equivalent or greater levels of proteasome inhibition**

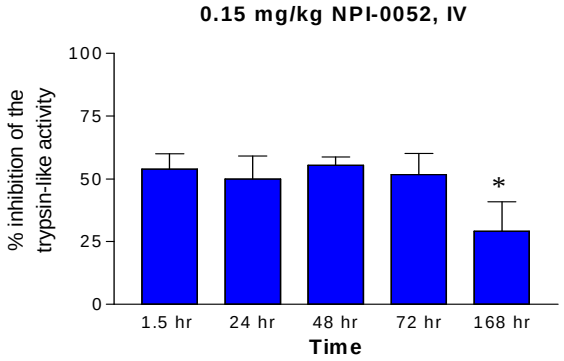
Unique activity profile:

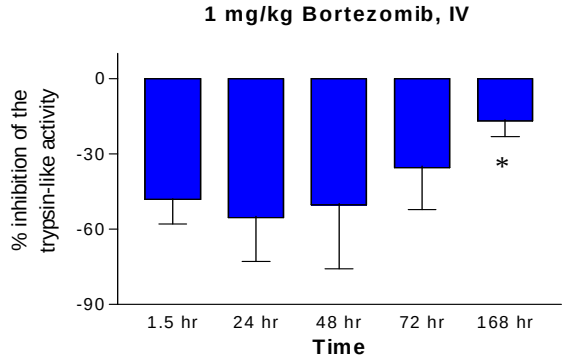
- **Efficacy in tumor models resistant to bortezomib**

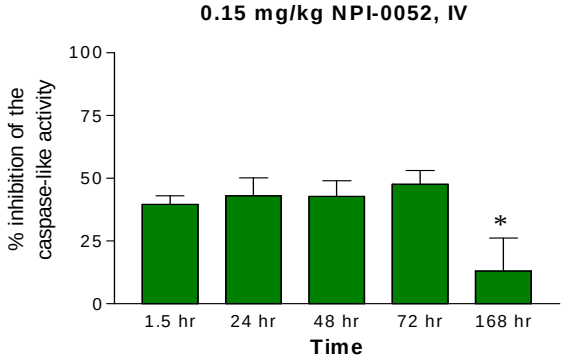
NPI-0052
Proteasome Inhibition Profile

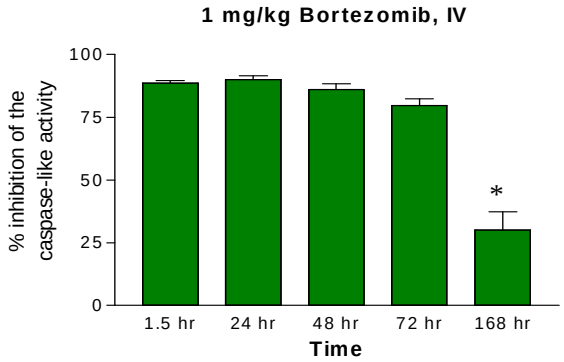


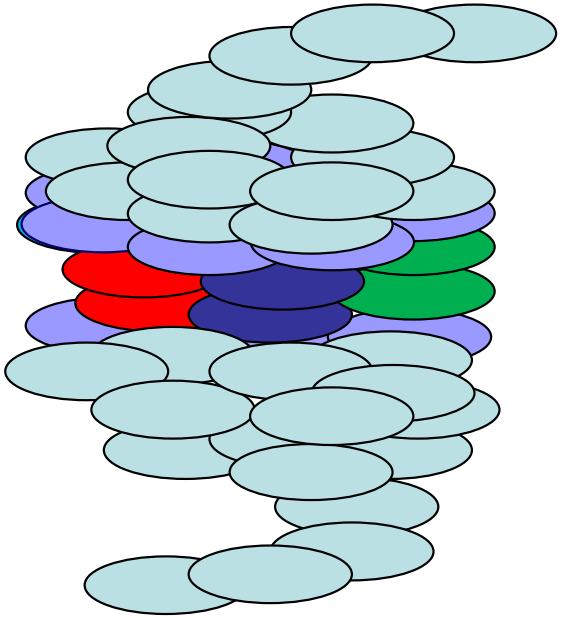








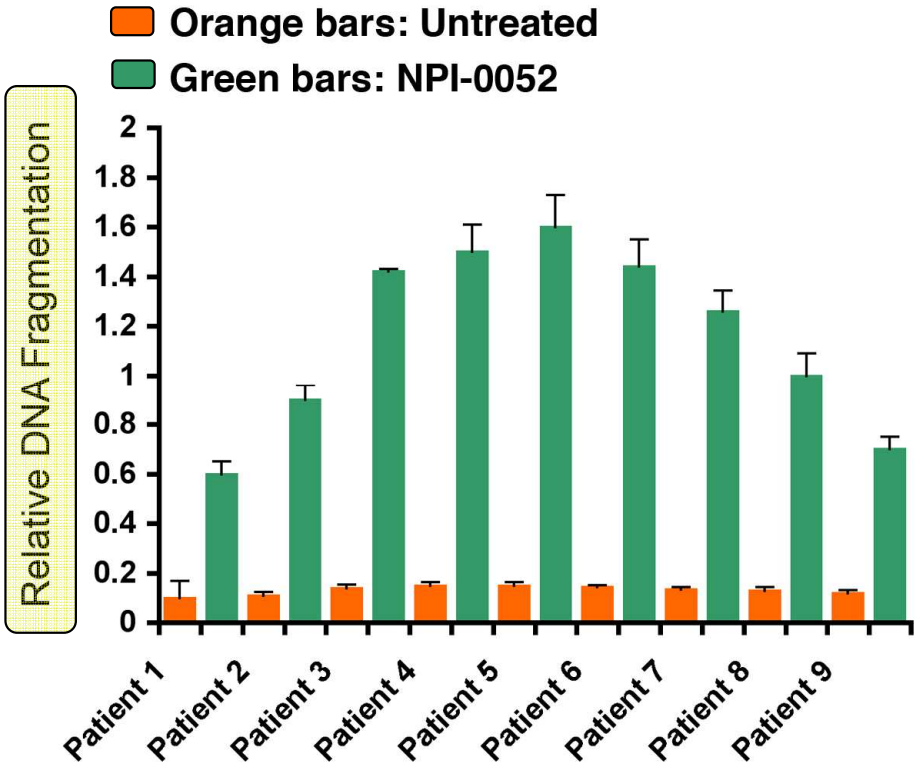




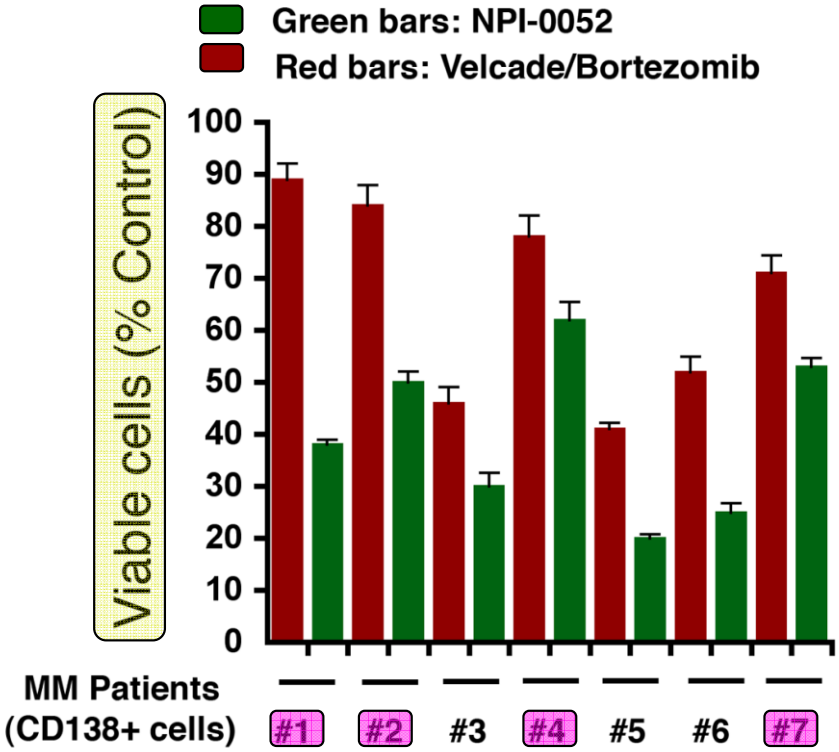
Chauhan et al., Cancer Cell 2005

NPI-0052 is Active in Bortezomib Resistant/Refractory Human MM Samples

MM cells from patients refractory to dexamethasone and thalidomide

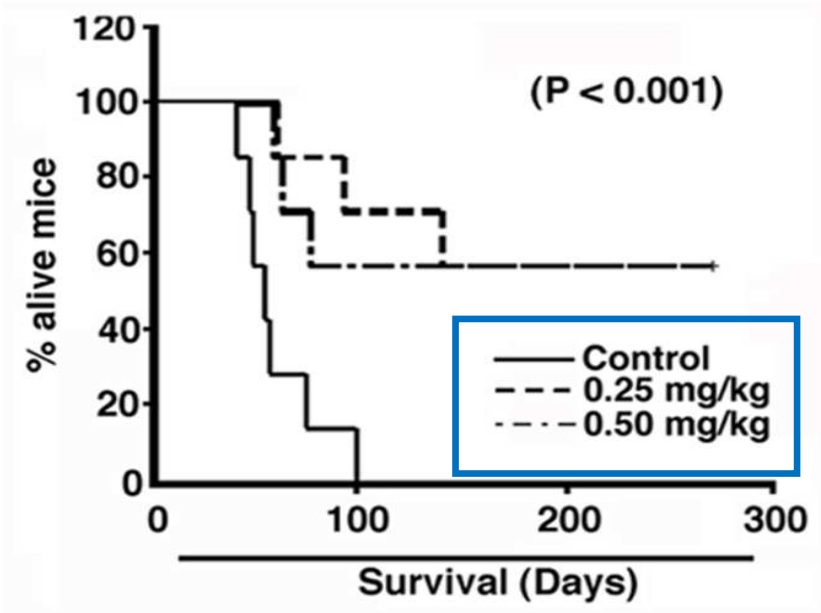


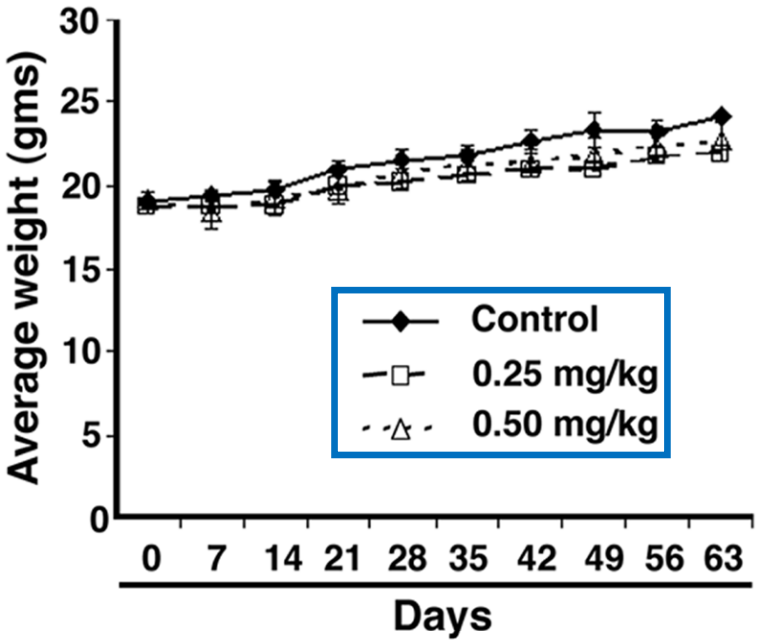
MM cells from patients also refractory to bortezomib



Chauhan et al., Cancer Cell 2005

Majority of Mice with Human MM.1S Myeloma Xenografts Tumor Free After NPI-0052

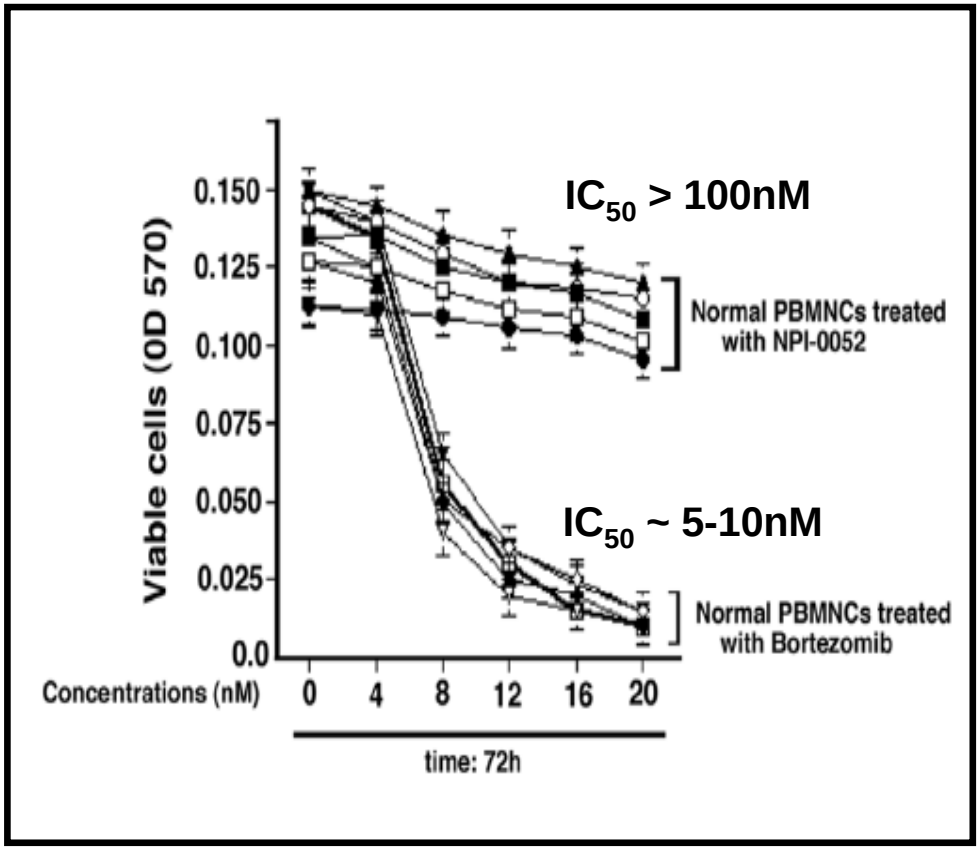




- NPI-0052 was administered orally BIW for 13 weeks
- NPI-0052 is well tolerated and prolongs survival with significantly reduced tumor recurrence
- Similar reduced tumor recurrence is obtained with NPI-0052 administered IV

Chauhan et al., Cancer Cell 2005

NPI-0052 Exhibits a Large Therapeutic Index



Human Cell Type	IC_{50} (nM)	
	NPI-0052	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

The average IC_{50} value of at least three experiments. Cells were treated for 48h.

Chauhan et al., Cancer Cell 2005

METHODS

Study design

- **Phase 1, open-label, trial in patients with relapsed or relapsed/refractory multiple myeloma.**
- **<u>Dosing Regimen</u>: 1-10 minute IV injection, Days 1, 8 and 15 in 4-week cycles**
- **<u>Escalation</u>: Accelerated Dose Titration**
  - **Dose escalation in 100% increments, until the first drug related ≥ Grade 2 toxicity, thereafter dose increments of ≤ 50% increments in cohorts of at least 3 patients.**
  - **Cohorts are expanded to 6 patients if a DLT is reported.**
- **RP2D cohort of 12 patients**
  - **Transition to a new lyophile formulation (lyophile with ~1/2 excipient volume of original liquid formulation).**
  - **Subset of intra-patient lyophile-liquid cross-over with comparative PK.**
- **PK: Cycle 1, D1 & D15.**
- **PD: Baseline: Cycle 1, D1 &15 and Day 15 every even cycle thereafter.**

Key Inclusion Criteria

- Karnofsky Performance Status (KPS) ≥ 70%.
- Relapsed or relapsed/refractory MM for which no other approved treatment is available and clinically indicated.
- All Adverse Events resulting from prior chemotherapy, surgery, or radiotherapy, must have resolved to CTCAE (v. 3.0) Grade ≤1 .
- Labs

  Hemoglobin ≥ 8 g/dL

  Absolute Neutrophil Count ≥ 1.0 x 10^9 /L

  Platelet count ≥ 50 x 10^9 /L

  Serum bilirubin ≤1.5 x ULN

  AST ≤2.5 x ULN

  Serum creatinine ≤ULN

  Creatinine clearance ≥ 50 mL/min

Key Exclusion Criteria

- Prior therapy within 28 days
- > Grade 1 proteinuria, untreated UTI, or pre-existing kidney disease
- Mucosal or internal bleeding and/or platelet refractory
- Hypersensitivity CTCAE Grade ≥ 3 to propylene glycol or ethanol
- Pregnant or breast-feeding
- Clinically significant co-morbid disease:
  - Active uncontrolled infection
  - Significant cardiac disease
  - Ongoing coagulopathies

NPI-0052-101

RESULTS

Demographics

	Patients (N=32)
Median age (years)	61
Male/Female	20 / 12
KPS 80 -100 70	27 4
Myeloma Subtype	Heavy Chain 17 IgG (53%) 7 IgA (21%) Light Chain 17 kappa (53%) 7 lambda (21%) Oligo-/Non-secretory 6 (19%)
Time from Initial Diagnosis (years)	5.5 (1.5 – 14.3)
Number of Prior Regimens (median) Prior SCT Prior Bortezomib Refractory to Prior Bortezomib*	5 (1 – 11) 20 (62%); 4 with >1 SCT (12%) 21 (66%) 11 (34%)

**No response on prior bortezomib-containing regimen OR progression on or within 60 days of last dose of bortezomib*

Enrollment

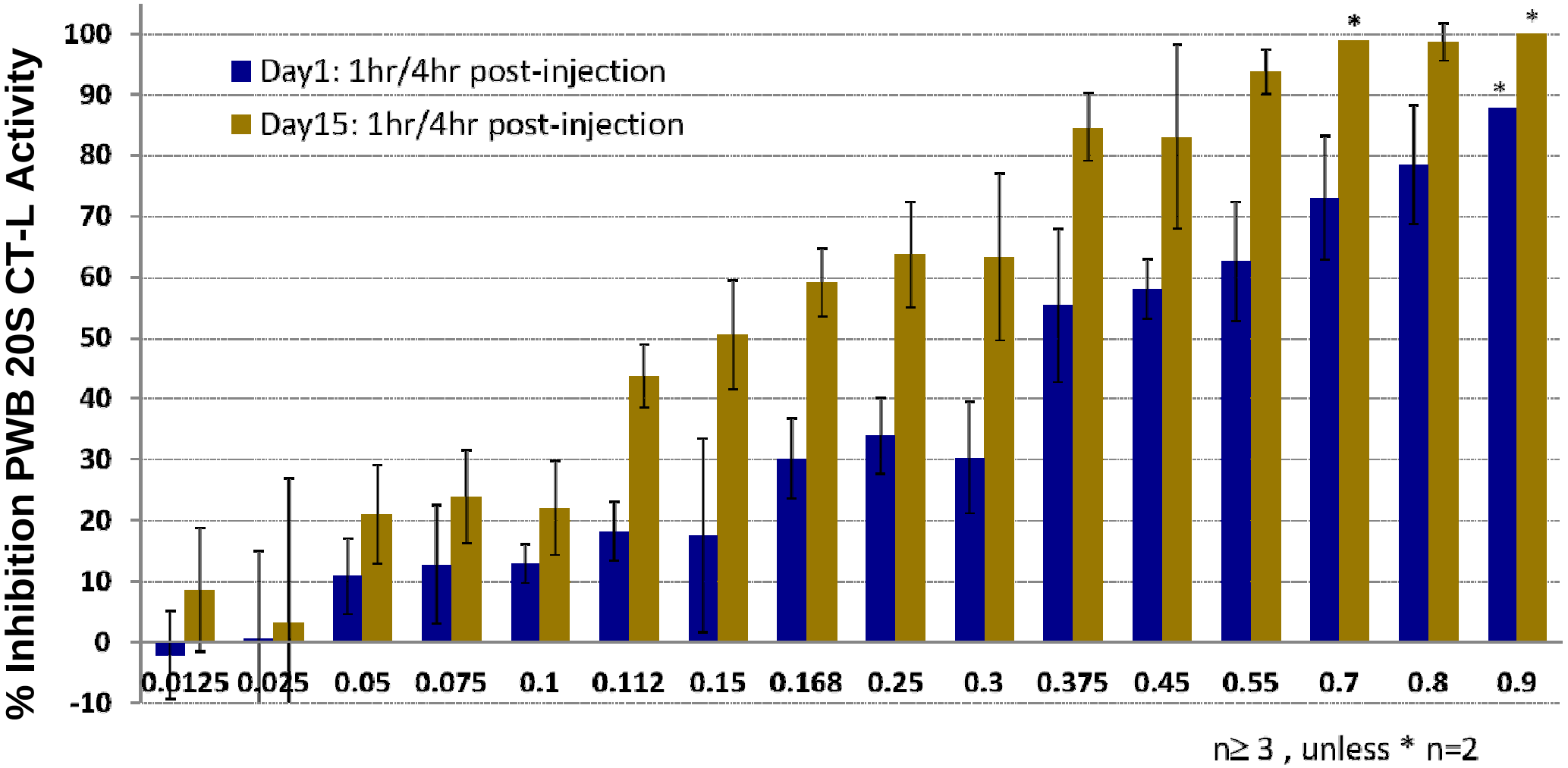
Cohort	Dose (mg/m^2)	# Patients
1	0.025	3
2	0.075	1
3	0.050	3
4	0.075	6
5	0.15	2
6	0.30	1
7	0.60	3
8	0.70	8
9	0.70 (Lyophile)	5

Adverse Events ≥10%

Adverse Event >10% of Patients	0.025 mg/m^2 (n=3)		0.05 mg/m^2 (n=3)		0.075 mg/m^2 (n=7)		0.15 mg/m^2 (n=2)		0.3 mg/m^2 (n=1)		0.6 mg/m^2 (n=3)		0.7 mg/m^2 (n=13)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Nausea	1				2				1		1		5	3*
Fatigue	2		1		3						1		5	1
Headache			2		1				1				7	
Diarrhoea	1						1		1				3	1
Vomiting	1				1						1		3	1
Dizziness			1		1						1		4	
Constipation	1				1						1		2	
Back Pain	1				2						1		1	
Anorexia			1										4	
Dyspnoea	1		2						1		1		1	
Upper repiratory tract infection	1		1		1				1		1			
Shoulder Pain					1		1				1		1	

As of 06 Nov 2009
*without prophylaxis

NPI-0052 Phase I Trials Summary
Proteasome Inhibition (CT-L in PWB)



Consolidated results from clinical trials NPI-0052-100, NPI-0052-101 and NPI-0052-102
PWB: Packed Whole Blood

Pharmacokinetics

- Dose related increases for Cmax and AUC_{total}
- Short half-life, mean < 10-15 minutes
- Large volume of distribution
- Rapid clearance
- Rapid (1-2 min) distribution from blood into organs and tissues, including tumor

Pharmacokinetics
Comparison of Formulations

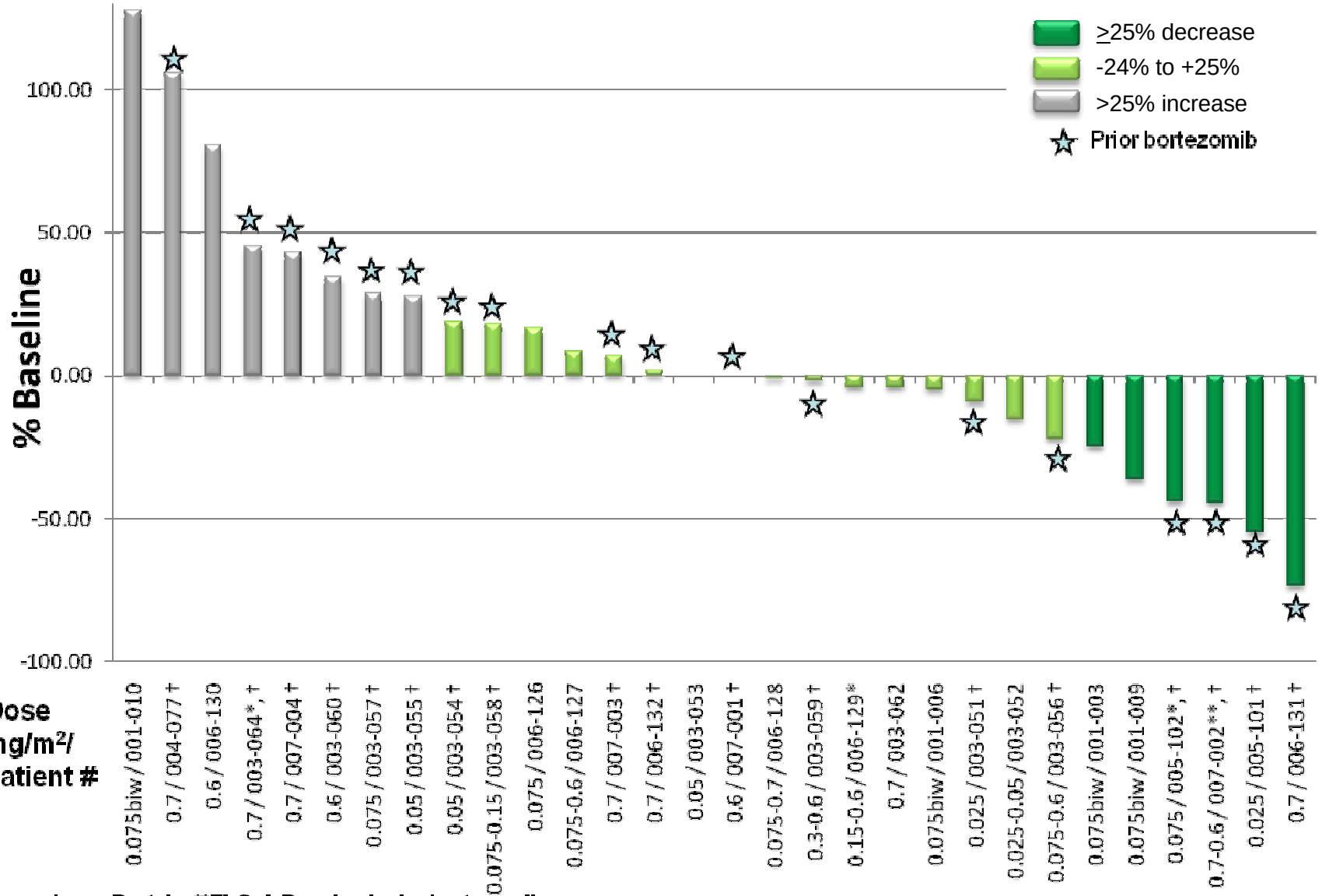
- **Subset with intra-patient cross-over comparison between liquid and lyophile formulations**
  - **0.7 mg/m^2 NPI-0052**
  - **sequence alternating between patients**

- **No appreciable difference between the liquid and lyophile formulations for pharmacokinetic parameters**

T1/2 Min		C_{MAX} ng/mL		AUC_{TOTAL} ng/mL*min		Clearance L/min		Vss L	
Liq	Lyo	Liq	Lyo	Liq	Lyo	Liq	Lyo	Liq	Lyo
7.7	6.8	66.8	56.4	442.9	461.3	3.45	3.23	39.6	31.1

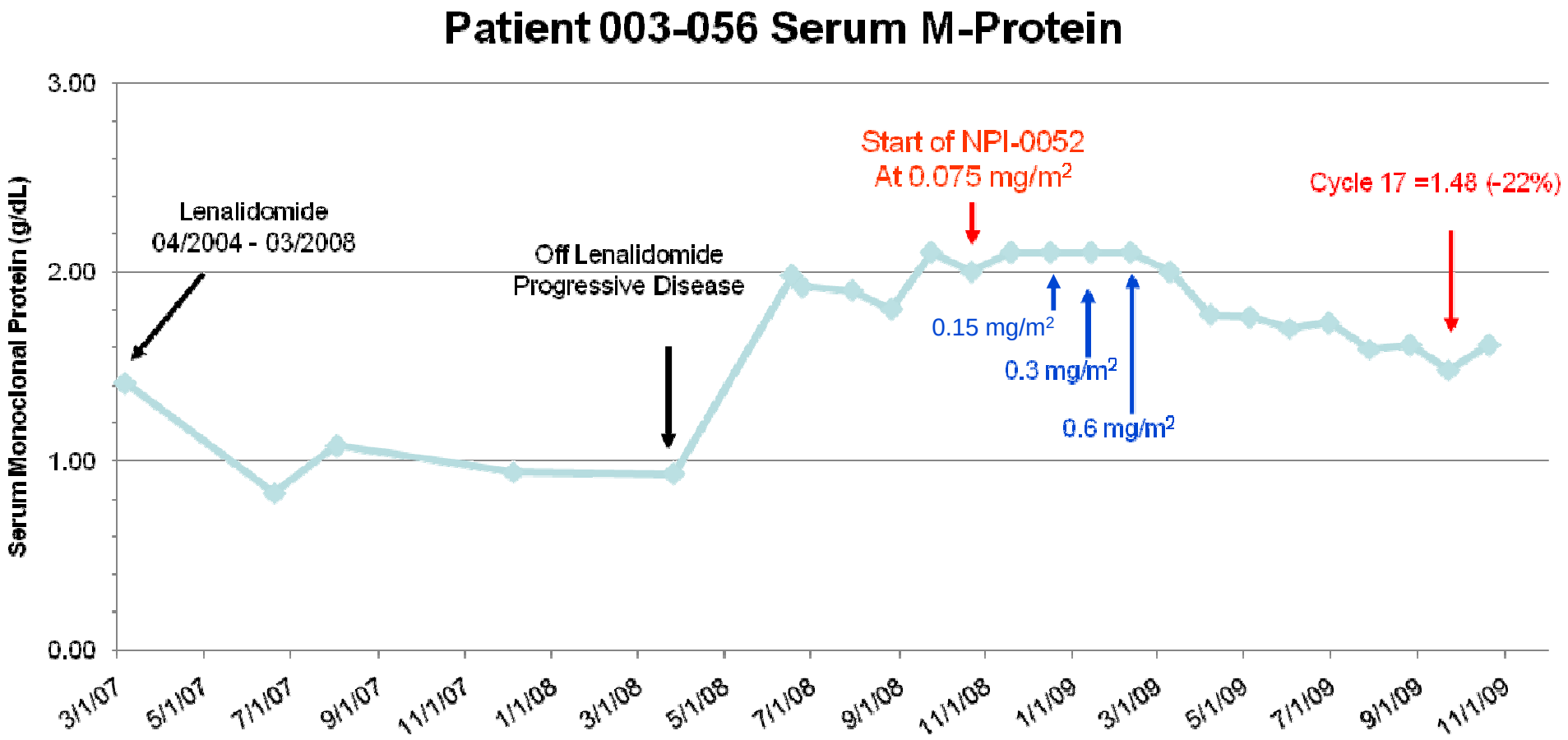
Data expressed as Mean of 2 patients

NPI-0052
M-Protein Best Response



*Bence Jones Protein; **FLC; † Received prior bortezomib

Patient 003-056



Patient 003-056 62 yo male, diagnosed in June 1998 (IgG); bortezomib responsive

12/98 – 03/99	Vincristine, Adriamycin, Dexamethasone (PD)
04/99 – 05/99	High dose Cyclophosphamide (PD)
01/00 – 06/00	Thalidomide (PR)
08/00 – 10/00	Alpha-interferon (PD)
11/00 – 12/00	Rituximab (PD)
02/01 – 08/01	Bortezomib, Dexamethasone (MR)
10/01 – 03/04	2-methoxyestradiol (SD)
04/04 – 03/08	Lenalidomide (PR)
07/08 – Present	NPI-0052 (0.6 mg/m^2) (SD)

Starting dose: 0.075 mg/m^2
Dose escalations: 0.15 mg/m^2 in Cycle 7
0.3 mg/m^2 in Cycle 8
0.6 mg/m^2 in Cycle 9
Patient continuing on study.

Conclusions

- **Escalation to the RP2D (0.7 mg/m^2) elicited in clinical trials in multiple myeloma patients was accomplished in this study and this dose is currently being assessed with a new lyophile formulation.**

- **NPI-0052 is generally tolerable at doses below the MTD.**
  - **Common AEs: fatigue, nausea/vomiting, dizziness, headache**
  - **NPI-0052 does not appear to induce neuropathy, neutropenia or thrombocytopenia.**

- **Preliminary PK data indicate dose dependence exposure, short elimination half life, rapid clearance and large volume of distribution. The liquid and lyophile formulations do not appear to differ in termss of pharmacokinetic parameters.**

- **Across all studies performed with NPI-0052:**
  - **Inhibition of proteasome activity into the predicted minimum effective range has been seen at doses ≥ 0.15 mg/m^2.**
  - **Inhibition is dose and time dependent, and reaches or exceeds that obtained with efficacious doses of bortezomib without producing the adverse event profile reported with bortezomib.**
  - **Therapeutic ratio potentially in the range of 2-6 fold.**

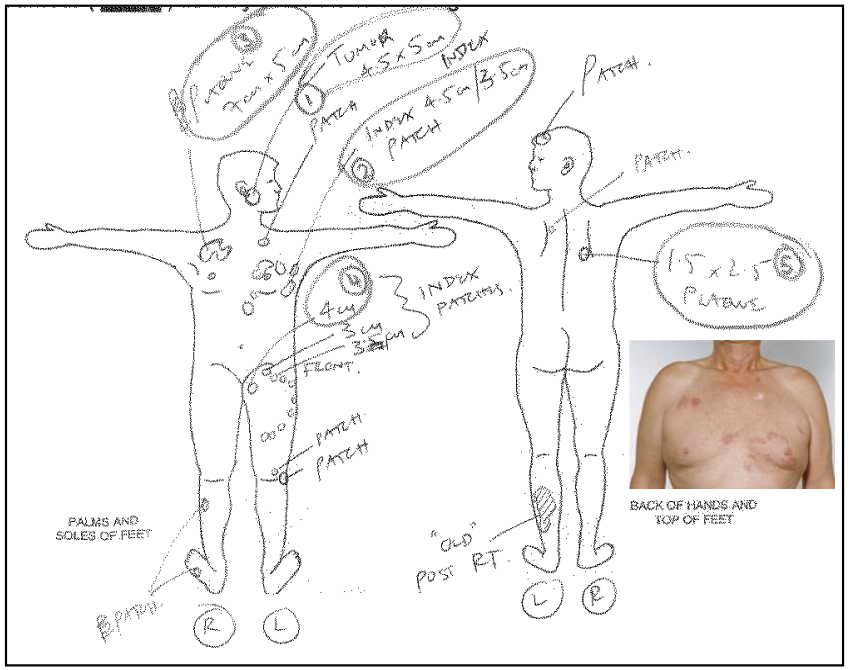
- **Clinical benefit is evidenced by decreases in M-Protein, with a significant proportion having failed bortezomib therapy.**

- **NPI-0052 continues to be assessed in multiple studies in myeloma, lymphoma, leukemia and solid tumors, weekly and twice-weekly, alone and in combination.**

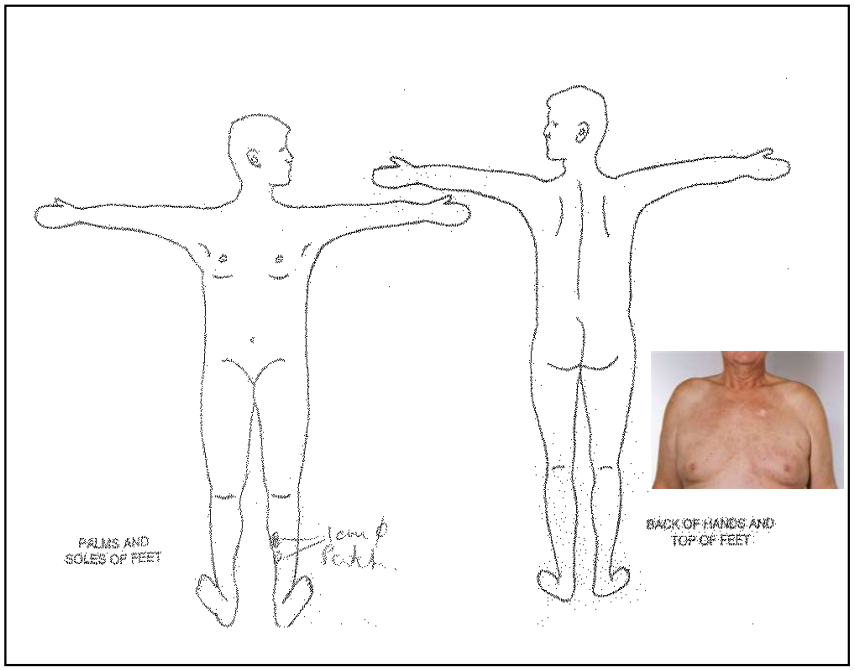
Example: Cutaneous MZL
Patient NPI-0052-102-004-004

Skin Lesion Maps

Baseline



Cycle 4



*Prior Therapy: rituximab, R-HyperCVAD
On Study NPI-0052-102 at 0.7 mg/m^2 NPI-0052

Presented: Sunday, December 6, 2009; 6:00 PM - 8:00 PM; Hall E Poster Board no. ***II-669***

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