The investigational agent MLN9708, an oral proteasome inhibitor, in patients with relapsed and/or refractory multiple myeloma (MM): results from the expansion cohorts of a phase 1 dose-escalation study

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Background

- The validity of proteasome inhibition as an anticancer strategy has been demonstrated with the first-in-class agent bortezomib[1–3]
  - Novel proteasome inhibitors are currently being developed with the aim of improving activity in multiple tumor types[4,5]
- MLN9708 is an orally bioavailable, potent, reversible, specific inhibitor of the 20S proteasome[6]
  - Citrate ester immediately hydrolyzes to MLN2238, biologically active dipeptidyl leucine boronic acid[6]
  - Similar selectivity and potency, dissociates from proteasome faster, and has greater tissue penetration compared with bortezomib in preclinical studies[3]
  - Demonstrated antitumor activity in solid tumor and hematologic malignancy xenograft models,[6–8] including in vivo models of MM
- MLN9708 is the first oral proteasome inhibitor to enter clinical investigation in MM
  - Here we report results from the expansion cohorts of a phase 1 dose-escalation study of oral MLN9708 in patients with relapsed or relapsed and refractory MM

1. Richardson PG, et al. N Engl J Med 2005;352:2487–98.
2. San Miguel JF, et al. N Engl J Med 2008;359:906–17.
3. Fisher RI, et al. J Clin Oncol 2006;24:4867–74.
4. Orlowski RZ and Kuhn DJ. Clin Cancer Res 2008;14:1649–57.
5. Dick LR, Fleming PE. Drug Discov Today 2010;15:243–9.
6. Kupperman E, et al. Cancer Res 2010;70:1970–80.
7. Lee EC, et al. Clin Cancer Res 2011; e-pub ahead of print.
8. Chauhan D, et al. Clin Cancer Res 2011;17:5311–21.

Study objectives (NCT00932698)

- **Primary objectives:**
  - **Safety profile/tolerability of MLN9708**
  - **Maximum tolerated dose (MTD)**
- **Secondary objectives:**
  - **Overall response rate (ORR; complete plus partial response [CR+PR])**
    - **In specific expansion cohorts**
  - **To characterize pharmacokinetics of MLN2238**
  - **To characterize pharmacodynamics (20S proteasome inhibition in blood – marker of target engagement)**

Study design

Oral MLN9708 administered on D 1, 4, 8, and 11 of a 21-day cycle, for up to 12 cycles

Dose-escalation cohorts

Dose-escalation: 3+3 schema, based on Cycle 1 DLTs

(modified Fibonacci dose sequence)

0.24→0.48→0.8→1.2→1.68→2.23→2.0 mg/m^2

↓

MTD established

Expansion cohorts

Relapsed and refractory cohort

Refractory to most recent therapy (PD while on therapy or within 60 days after last dose of therapy)

Bortezomib-relapsed cohort

Relapsed after previous bortezomib therapy but not refractory

Proteasome inhibitor-naïve cohort

Relapsed after ≥1 therapy, must include an IMiD and corticosteroids, no PI

Prior carfilzomib cohort

Received prior carfilzomib and with relapsed or refractory disease

IMiD=immunomodulatory drug; PD=progressive disease

Patients

- Inclusion criteria:
  - Age ≥18 yrs
  - ECOG performance status of 0–2
  - For dose-escalation cohorts: relapsed/ refractory MM after ≥2 prior therapies, which must have included bortezomib, thalidomide or lenalidomide, and corticosteroids
    - Pts could have received other proteasome inhibitors
  - In the 4 expansion cohorts, various criteria permitted (PI exposed, naïve, refractory)
  - Measurable disease (serum M-protein ≥1 g/dL or urine M-protein ≥200 mg/24 hours)
- Exclusion criteria:
  - G ≥2 peripheral neuropathy (PN)
  - G ≥2 diarrhea
- Concomitant corticosteroid use prohibited
- Prednisone ≥ 10mg or equivalent prohibited

Assessments

- Adverse events (AEs) graded per NCI CTCAE v3.0
- DLTs defined as the following AEs during cycle 1 considered related to MLN9708:
  - G4 thrombocytopenia or neutropenia lasting >7d, or platelets <10,000 mm^3 at any time
  - G3 neutropenia with fever and/or infection, or G3 thrombocytopenia with clinically significant bleeding
  - G ≥3 non-hematologic toxicity
  - G2 PN with pain
- Blood samples collected after dosing on D1 and 11, cycle 1, for PK/PD analyses
  - PK/PD parameters calculated using non-compartmental methods (WinNonlin software v5.3)
- Response assessed using the IMWG uniform criteria[1] plus
  - Minimal response (MR)[2] and nCR[3]

1. Durie et al Leukemia 2006; 2. Bladé et al BJH 1998, 3. Richardson et al NEJM 2003

Patient enrollment

- As of October 21, 2011, 56 pts have been enrolled
  - 26 to dose-escalation cohorts at MLN9708 doses of 0.24–2.23 mg/m^2
    - MTD determined to be 2.0 mg/m^2
  - 36 to expansion cohorts (includes 6 from dose-escalation MTD cohort)
    - 17 to relapsed and refractory (RRMM) cohort
    - 14 to bortezomib-relapsed cohort
    - 5 to proteasome inhibitor (PI)-naïve cohort
    - 0 to prior carfilzomib cohort

Patient characteristics

Characteristics	Dose-escalation cohorts (n=26)	Expansion cohorts (n=36)*	Total (N=56)
Median age, years (range)	65 (50–83)	65.5 (50–86)	65.5 (50–86)
Male, %	62	44	52
White / African American / Other, %	85 / 15 / 0	97 / 0 / 3	91 / 7 / 2
Median time since MM diagnosis, years (range)	4.7 (1.1–24.3)	4.8 (1.5–12.6)	4.7 (1.1–24.3)
Median no. prior lines of therapy (range)	4 (2–28)	4 (1–12)	4 (1–28)
Bortezomib, %	100	81	88
Lenalidomide, %	85	75	79
Thalidomide, %	58	64	59
Carfilzomib/Marizomib, %	4	8	7
ASCT, %	62	53	57
Refractory to last therapy, %	58	53	52
Bortezomib-refractory,† %	27	32	28

*Includes 6 pts from MTD dose-escalation cohort. †On last prior therapy.

Treatment exposure

- Pts have received a median of 3.5 (range 1–23) treatment cycles
  - 19 (34%) treated for ≥6 cycles
  - 8 (14%) treated for ≥12 cycles
- At data cut-off, 12 (21%) pts remain on study treatment
  - 44 (79%) have discontinued, mainly due to PD (n=31, 55%)

MLN9708 safety profile

AE	Dose-escalation cohorts (n=26)	Expansion cohorts (n=36)*	Total (N=56)
Any AE	100%	97%	98%
Any drug-related AE	88%	94%	91%
Any grade ≥3 AE	65%	78%	73%
Any drug-related grade ≥3 AE	50%	67%	61%
Any serious AE (SAE)	42%	61%	52%
Any drug-related SAE	19%	33%	27%
Dose reduction due to AEs	27%	33%	32%
Discontinuation due to AEs	4%	14%	9%
On-study death	4%	3%	4%

*Includes 6 pts from MTD dose-escalation cohort

Drug-related AEs in >20% of patients overall

AE	Dose-escalation cohorts (n=26)	Expansion cohorts (n=36)*	Total (N=56)
Fatigue	42%	44%	46%
Thrombocytopenia	31%	47%	39%
Nausea	31%	33%	30%
Diarrhea	35%	17%	23%
Vomiting	23%	22%	23%
Rash†	23%	19%	21%

*Includes 6 pts from MTD dose-escalation cohort. †Rashes, eruptions, and exanthems NEC, including rash macular, rash, and rash macro-papular

- Drug-related G ≥3 AEs in ≥ 2 pts include:
  - Thrombocytopenia (n=19), neutropenia (n=8), fatigue (n=5), rash (all terms, n=5), abdominal pain, anemia, hypophosphatemia, and leukopenia (each n=2)

Peripheral neuropathy

- 6 (11%) pts had drug-related PN
  - 4 G1, 2 G2
- All pts had G1 PN as baseline at study entry
  - 1 pt treated at 0.8 mg/m^2 and 1 treated at the MTD of 2.0 mg/m^2 reported worsening to G2
  - 1 pt treated at 1.68 mg/m^2 and 3 treated at the MTD of 2.0 mg/m^2 reported worsening to G1
- No G ≥3 PN reported with oral MLN9708

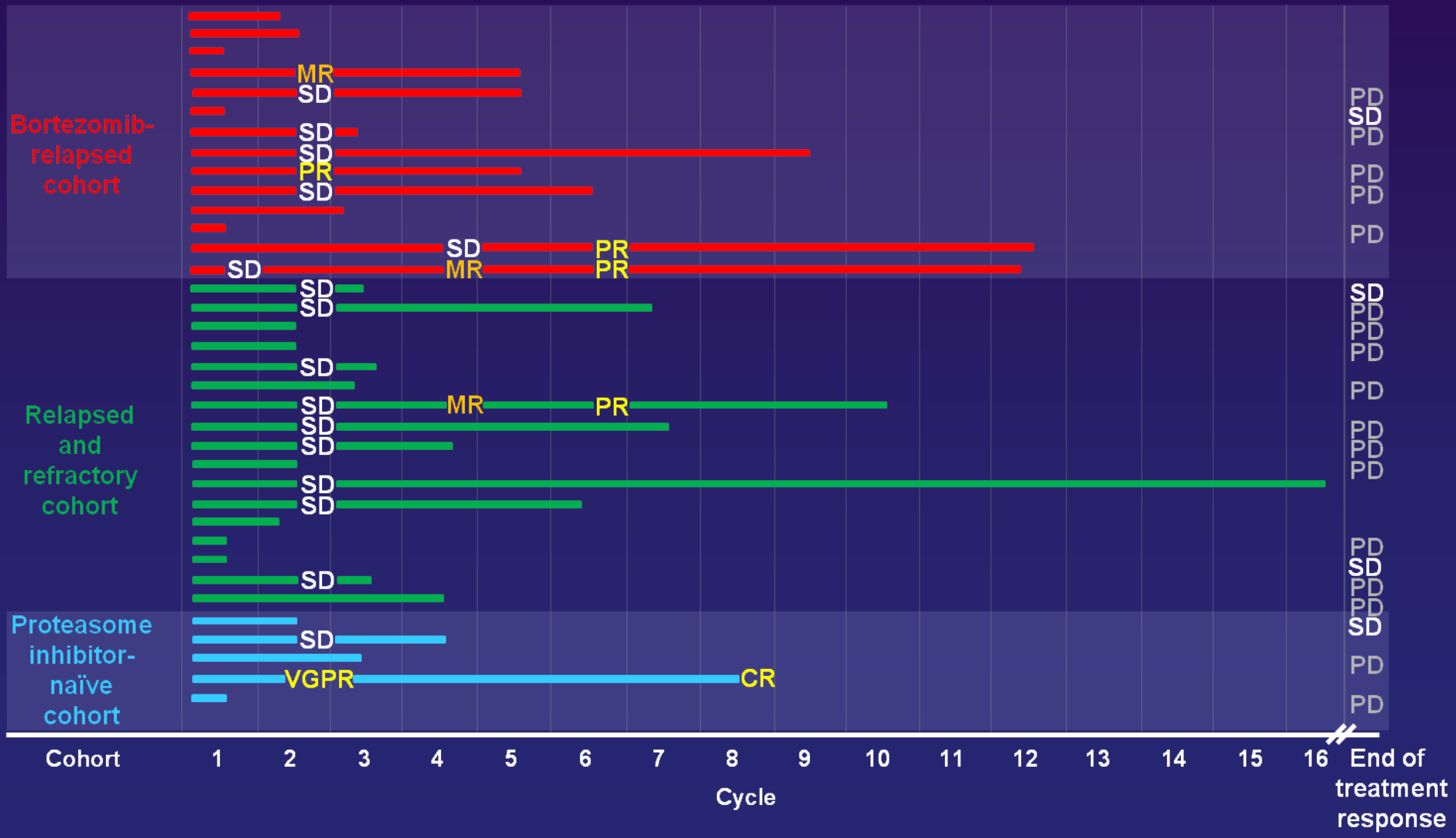
Dose Reductions and Discontinuations

- Dose reductions due to AEs were required for 18 (32%) pts
  - Most commonly (in ≥2 pts) due to thrombocytopenia, rash, and neutropenia
- Discontinuations due to AEs were required for 5 (9%) pts
  - Due to thrombocytopenia (cycle 1), pulmonary hypertension (cycle 1), and pruritic rash (cycle 4), as well as spinal cord compression (cycle 1) and bone pain (cycle 3) due to PD
- Two pts died on study
  - Due to an undiagnosed cardiac disorder (reported as unrelated to MLN9708) in a pt with atrial fibrillation, and a history of syncope and orthostatic hypotension, receiving MLN9708 0.8 mg/m^2
  - Due to PD (reported as unrelated to MLN9708) in a pt in the MTD relapsed and refractory expansion cohort

Preliminary Response Analysis

- 46 pts evaluable for response
  - 21 in dose-escalation cohorts
  - 30 in expansion cohorts (including 6 from dose-escalation cohorts)
- 6 pts have achieved ≥PR
  - 1 CR, confirmed by bone marrow (PI-naïve expansion cohort)
  - 5 PRs (1 each at 1.2 and 2.23 mg/m^2 in dose-escalation cohorts; 1 in RRMM and 2 in bortezomib-relapsed expansion cohorts)
- 1 pt achieved MR (bortezomib-relapsed expansion cohort; 40% M-protein reduction)
- All 7 pts remain in response, with duration of disease control of up to 15.9 months
- 28 pts have achieved SD
  - 14 in dose-escalation cohorts
  - 9, 5, and 2 in RRMM, bortezomib-relapsed, and PI-naïve expansion cohorts
  - Durable, with disease stabilization for up to 12.9 months

MLN9708 treatment duration and response – expansion cohorts



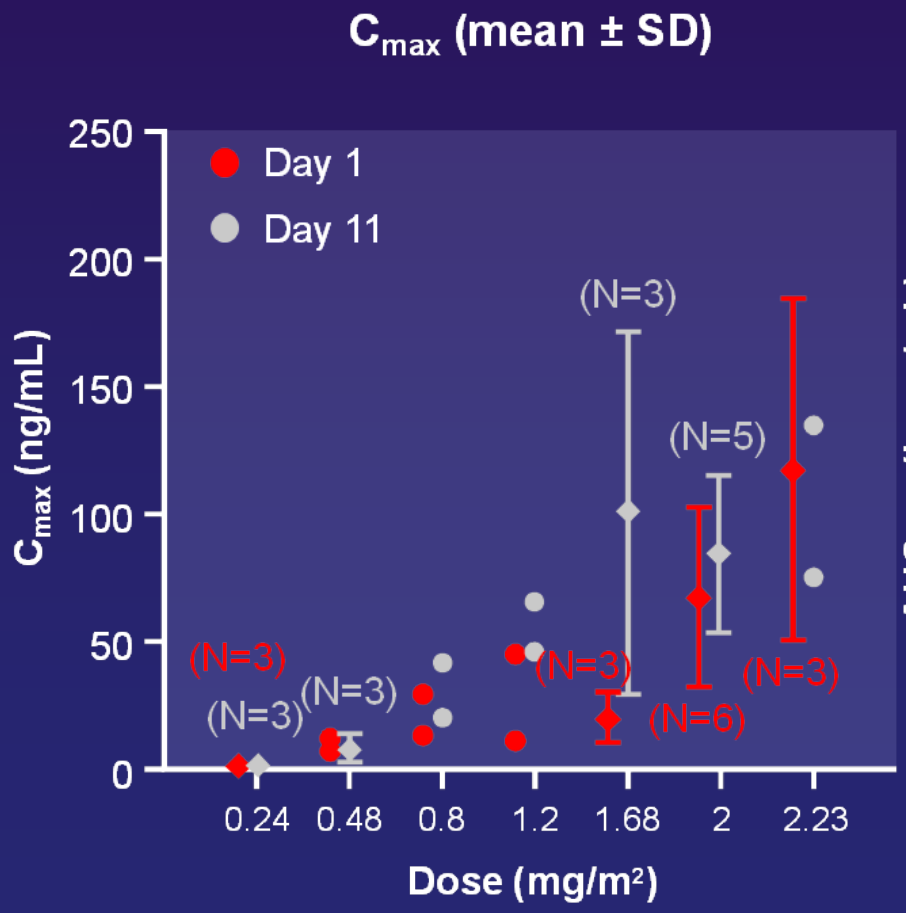
Pharmacokinetics / Pharmacodynamics

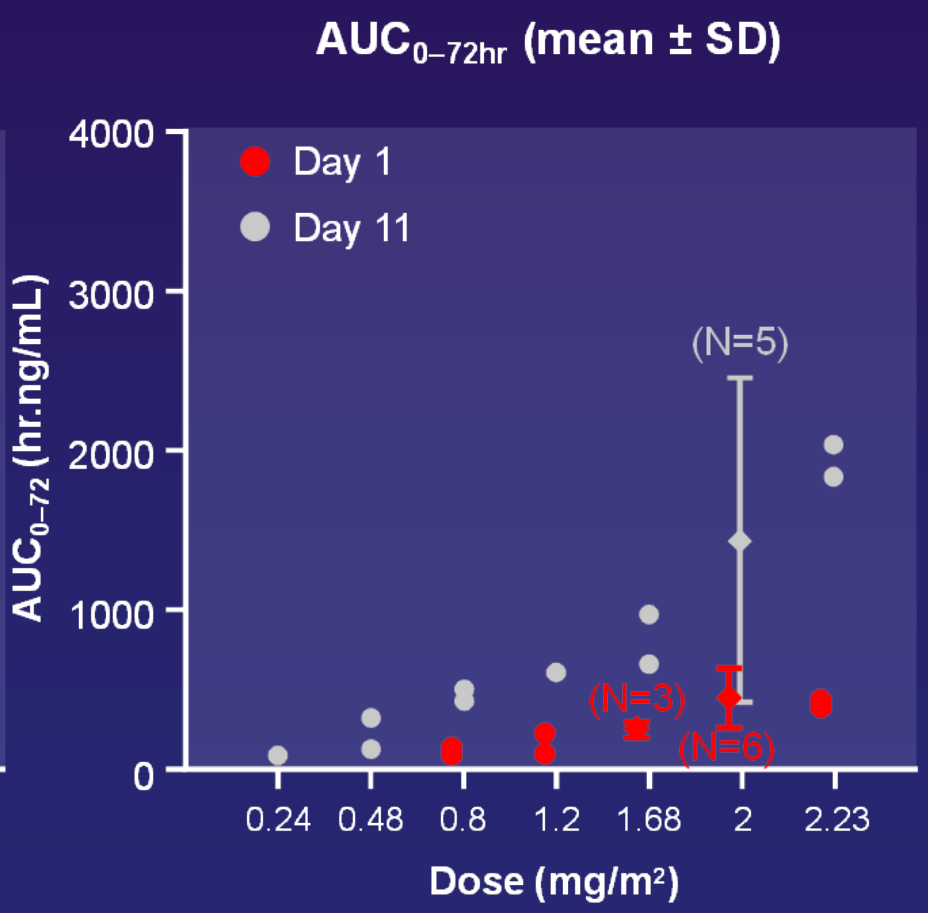
- MLN9708 was rapidly absorbed; MLN2238 T_{max} was 0.5–1.25 hours
- MLN2238 terminal half-life of approximately 4–6 days after multiple MLN9708 dosing
- Dose-dependent increase in whole blood 20S proteasome inhibition observed[1]

1. Gupta N, et al. Haematologica 2011;96(suppl 1):S88 (abstract P-197).

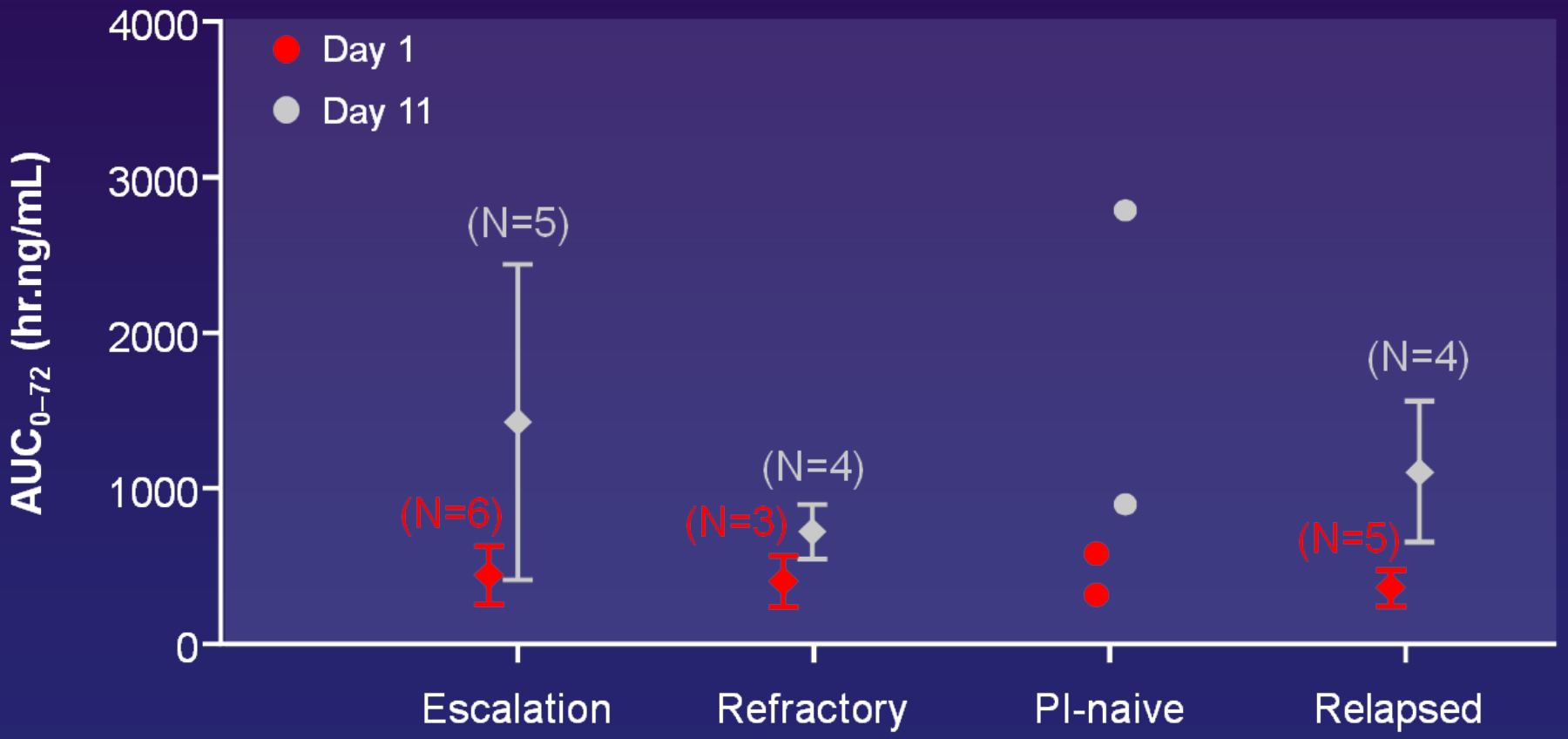
MLN2238 C_{max} and AUC in the dose-escalation cohorts on days 1 and 11

- MLN2238 plasma exposure appeared to increase proportionally with increasing MLN9708 dose from 0.8–2.23 mg/m²





MLN2238 AUC (mean ± SD) in the expansion cohorts on days 1 and 11



- **Exposures appeared to be similar across all expansion cohorts after 2.0 mg/m² MTD dose**

Conclusions

- MLN9708 is the first orally available PI to enter clinical investigation in MM pts
- MTD established as 2.0 mg/m^2 on twice-weekly dosing
  - Data from a once weekly phase 1 dose-escalation study in RRMM will be presented at this meeting[1]
- Oral MLN9708 generally well tolerated
  - Infrequent PN, and no G 3/4 PN observed
  - Frequency/severity of PN promising relative to bortezomib in RRMM
- PK/PD properties support continued development
  - Terminal half-life of 4–6 days supports twice-weekly dosing
  - Plasma exposures increase proportionally with dose
  - Dose-dependent 20S proteasome inhibition in blood
- Preliminary data suggest activity in heavily pretreated RRMM
  - Including durable responses and disease control

1. Kumar, et al. ASH 2011, abstract #816

Future directions

- **Combination trials ongoing**
  - **Oral MLN9708 plus lenalidomide and low-dose dexamethasone in pts with newly diagnosed MM (NCT01217957)[1]**
  - **Oral MLN9708 plus melphalan–prednisone in pts with newly diagnosed MM (NCT01335685)**
- **Studies ongoing in other hematologic malignancies**
  - **Single-agent IV MLN9708 in pts with relapsed/refractory lymphoma (NCT00893464) [2]**
  - **Single-agent oral MLN9708 in pts with relapsed/refractory light-chain amyloidosis (NCT01318902)**

1. Berdeja, et al. ASH 2011, abstract #479
2. Assouline et al ASH 2011, abstract #2672

Acknowledgments

- All patients included in this study and their families
- All physicians, research nurses, study coordinators, and research staff participating in this study
- Dennis Noe of Millennium Pharmaceuticals, Inc.
  - The authors would also like to acknowledge the writing assistance of Steve Hill of FireKite during the development of this presentation, which was funded by Millennium Pharmaceuticals, Inc.