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

Paul G. Richardson,1 Rachid Baz,2 Michael Wang,3 Andrzej J. Jakubowiak,4 Deborah Berg,5 Guohui Liu,5 Neeraj Gupta,5 Alessandra Di Bacco,5 Ai-Min Hui,5 Sagar Lonial6

1Dana-Farber Cancer Institute, Boston, MA, USA; 2H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; 3M. D. Anderson Cancer Center, Houston, TX, USA; 4University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; 5Millennium Pharmaceuticals, Inc., Cambridge, MA, USA; 6Winship Cancer Institute of Emory University, Atlanta, GA, USA
Background

• The validity of proteasome inhibition as an anticancer strategy has been demonstrated with the first-in-class agent bortezomib\textsuperscript{1–3}
  – Novel proteasome inhibitors are currently being developed with the aim of improving activity in multiple tumor types\textsuperscript{4,5}

• MLN9708 is an orally bioavailable, potent, reversible, specific inhibitor of the 20S proteasome\textsuperscript{6}
  – Citrate ester immediately hydrolyzes to MLN2238, biologically active dipeptidyl leucine boronic acid\textsuperscript{6}
  – Similar selectivity and potency, dissociates from proteasome faster, and has greater tissue penetration compared with bortezomib in preclinical studies\textsuperscript{3}
  – Demonstrated antitumor activity in solid tumor and hematologic malignancy xenograft models,\textsuperscript{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

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: 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/m²

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\textsuperscript{1} plus
  – Minimal response (MR)\textsuperscript{2} and nCR\textsuperscript{3}

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/m²
    • MTD determined to be 2.0 mg/m²

  – 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

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

*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

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

*Includes 6 pts from MTD dose-escalation cohort
Drug-related AEs in >20% of patients overall

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

*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/m² and 1 treated at the MTD of 2.0 mg/m² reported worsening to G2
  - 1 pt treated at 1.68 mg/m² and 3 treated at the MTD of 2.0 mg/m² 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/m²
  – 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/m² 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
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$^1$

---

MLN2238 $C_{\text{max}}$ 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/m$^2$
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/m² on twice-weekly dosing
  — Data from a once-weekly phase 1 dose-escalation study in RRMM will be presented at this meeting¹

• 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.