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MLN9708
Clinical Study Report C16004 Synopsis

C16004 FINAL CLINICAL STUDY REPORT SYNOPSIS

Study Title: An Open-Label, Dose-Escalation, Phase 1 Study Evaluating the Safety and Tolerability of Weekly Dosing of the Oral Form of MLN9708, a Second-Generation Proteasome Inhibitor, in Adult Patients With Relapsed and Refractory Multiple Myeloma

Investigator(s): PPD

Study Center(s): 6 centers in the United States (1 other center did not screen or enroll patients)

Publications (reference):


Phase: 1
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Initiation Date (first patient enrolled): 31 October 2009  

Early Termination Date: 18 September 2012 (Closed enrollment early as study met primary objectives.)  

Completion Date (last patient completed): 3 patients still ongoing as of database lock on 28 Feb 2013; 1 patient still on treatment as of 9 December 2013  

Study Objectives:  

Primary Objectives  
- To determine the safety profile, tolerability, and maximum tolerated dose (MTD) of MLN9708 administered orally on a weekly dosing schedule in patients with relapsed and/or refractory multiple myeloma (RRMM)  

Secondary Objectives  
- To characterize the pharmacokinetics (PK) in plasma of MLN9708 administered orally  
- To characterize the pharmacodynamic effect on 20S proteasome activity in blood of MLN9708 administered orally  
- To determine the ORR and the CR + PR + MR rate of MLN9708 in patients with RRMM who are either proteasome inhibitor (PI)–naïve, have relapsed after VELCADE therapy, or who had recently been treated with carfilzomib  

METHODS  

Design: This phase 1, open-label, multicenter, dose escalation study evaluated the safety profile, MTD, and early activity of weekly dosing of the oral formulation of MLN9708 in adult patients with RRMM. The patients treated during the dose escalation portion had relapsed after receiving at least 2 prior lines of therapy that had to include some combination of VELCADE® (bortezomib) for Injection, immunomodulatory drugs (IMiDs), and corticosteroids. After determination of the MTD, other patients were enrolled in 1 of 4 MTD expansion cohorts (as defined below) to more fully understand the activity of MLN9708 in patients who represented the highly heterogeneous population seen in clinical practice during the conduct of this study; in the expansion cohorts, patients had to have been previously treated with at least 1 line of therapy involving VELCADE, thalidomide or lenalidomide, or corticosteroids.  

Patients were administered MLN9708 orally once weekly, on Days 1, 8, and 15 of a 28-day treatment cycle, at a starting dose of 0.24 mg/m², on the basis of findings in animal toxicology studies. A 3+3 dose escalation scheme was then used to determine the MTD and followed a modified Fibonacci sequence to guide escalation with doses of 2.0-, 1.67-, 1.50-, 1.40-, and 1.33-fold over the previous dose level thereafter. The MTD was defined as the highest dose that generated a dose-limiting toxicity (DLT) rate of 0 of 6 or 1 of 6 patients during Cycle 1. Although DLTs could have occurred at any point during treatment, including during cycles after Cycle 1, only DLTs that occurred during Cycle 1 influenced decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Once the MTD was established, patients were enrolled into the 4 expansion cohorts to further characterize the safety, tolerability, and efficacy of MLN9708.  

Number of Patients (planned and analyzed): Approximately 70 patients were planned to be enrolled in this study. Each planned dose level started with the treatment of 3 patients. The next cohort of 3 patients was only treated after the previous cohort of 3 patients completed Cycle 1; when necessary, according to the DLT escalation rules, up to 3 additional patients were enrolled to a dose
level. Once the MTD was established, 10 additional patients were to be enrolled into the Relapsed and Refractory MTD expansion cohort, approximately 6 patients were to be enrolled into the Carfilzomib MTD expansion cohort, approximately 6 patients were to be enrolled into the PI-Naïve MTD expansion cohort, and approximately 12 patients were to be enrolled into the VELCADE-Relapsed MTD expansion cohort. The final analysis included 60 evaluable patients for safety, 44 for PK assessment, 48 for pharmacodynamic assessment, and 50 for efficacy.

**Diagnosis and Main Criteria for Inclusion:** Eligible male and female patients were those who had a diagnosis of multiple myeloma (MM) with measurable disease defined by at least 1 of the following measurements: serum M-protein ≥ 1 g/dL (≥ 10 g/L) (or for dose escalation cohorts, ≥ 0.5 g/dL [≥ 5 g/L]) and/or urine M-protein ≥ 200 mg/24 hours. Patients had to be at least 18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. Patients had to have RRMM and prior treatment as follows:

- **Dose escalation cohorts:** Patients with RRMM after at least 2 prior lines of therapy that had to include some combination of VELCADE, IMiDs, and corticosteroids.
- **MTD expansion cohorts:** Patients with RRMM after at least 1 line of therapy involving VELCADE, thalidomide or lenalidomide, or corticosteroids.
- **Relapsed and Refractory cohort:** Patients who met requirements for dose escalation cohorts and were refractory to their most recent therapy as evidenced by progressive disease (PD) while on therapy or within 60 days after their last dose of therapy.
- **PI-Naïve cohort:** Patients with RRMM after prior therapy including thalidomide or lenalidomide and corticosteroids but who had never received a PI.
- **VELCADE-Relapsed cohort:** Patients with RRMM who had relapsed after previous VELCADE exposure (ie, were not refractory to VELCADE) and were not treated with any other PIs.
- **Carfilzomib cohort:** Patients who had previously received carfilzomib and had relapsed or were refractory to their most recent therapy (as evidenced by PD while on therapy or within 60 days after their last dose of therapy, respectively).

**Test Product and Dose and Mode of Administration:** MLN9708 was administered orally once weekly, on Days 1, 8, and 15 during a 28-day treatment cycle. The starting dose in the dose escalation segment was 0.24 mg/m² MLN9708. Subsequent doses administered were 0.48, 0.80, 1.20, 1.68, 2.23, 2.97, and 3.95 mg/m².

**Duration of Treatment:** The maximum duration of treatment planned was 12 months, unless it was determined that a patient would derive benefit from continued therapy beyond 12 months. Patients discontinued treatment if they experienced PD or unacceptable toxicities.

**Reference Therapy, Dose and Mode of Administration, Batch Number:** No reference or placebo treatment was used in this study. All eligible patients received treatment with an oral formulation of MLN9708.

**Pharmacokinetic Assessments:** MLN9708 (ixazomib citrate) is the citrate ester of the biologically active dipeptide boronic acid MLN2238 (ixazomib). Blood samples for the determination of plasma concentrations of MLN2238 were collected predose (within 1 hour before dosing) on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycle 2. Additional blood samples were collected after MLN9708 administration on Days 1 and 15 of Cycle 1: at 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 8 hours, 24 hours (ie, on Days 2 and 16), 48 hours (ie, on Days 3 and 17), and 96 hours (ie, on Days 5 and 19) postdose. Plasma concentrations of MLN2238 were measured using a validated liquid chromatography/tandem mass spectrometry assay. The maximum observed plasma
concentration of MLN2238 (C$_{\text{max}}$), the time of first observed C$_{\text{max}}$ (T$_{\text{max}}$), and the area under the MLN2238 concentration-time curve from time 0 to 168 hours postdose (AUC$_{0-168}$) were calculated after both Day 1 and Day 15 administration of MLN9708. The terminal phase half-life (t$_{1/2}$) and the accumulation ratio were also determined after the Day 15 dose.

**Pharmacodynamic Assessments:** Blood samples for the measurement of whole blood 20S proteasome activity were collected at the same time points as the PK samples. Whole blood 20S proteasome activity was measured using a fluorogenic assay. The maximum observed inhibition of 20S proteasome activity (E$_{\text{max}}$), time to first observed E$_{\text{max}}$, and the area under the 20S proteasome inhibition-time curve from time 0 to 168 hours post-dose (AUE$_{0-168}$) were determined after both Day 1 and Day 15 administration of MLN9708.

**Efficacy Assessments:** Disease response was assessed by the investigators according to the International Myeloma Working Group (IMWG) criteria with the addition of MR and near complete response (nCR) from the European Society for Blood and Marrow Transplantation criteria by investigators. Response assessments were performed every other treatment cycle beginning with Cycle 3, Day 1. Response categories were as follows: CR, stringent complete response, nCR, PR, very good partial response (VGPR), MR, stable disease (SD), and PD. Complete response was confirmed according to the IMWG criteria. PD could be confirmed per standard clinical practice with local laboratory results done at the site.

For patients with documented extramedullary disease, positron emission tomography-computed tomography, computed tomography, or magnetic resonance imaging was performed during screening for evaluation of disease. For patients enrolled in an MTD expansion cohort, if disease was documented at screening, the same imaging modality was repeated as required to document response or PD. A complete skeletal survey was performed at screening. If a patient had lytic lesions at screening, repeat imaging was done for symptoms or signs suggesting increased or new bone lesions, any time at the physician’s discretion, and at the End of Study (EOS) visit. Repeat and follow-up scans used the same imaging modality used at screening. Radiographs were analyzed locally, and reports were maintained with the patient records.

For the serum free light chain assay, immunofixation of serum and urine, and quantification of M-protein and immunoglobulins, blood and urine samples were obtained serially (blood only for the free light chain assay) at the Screening visit, on Cycle 1 Day 1, every other treatment cycle (beginning at Cycle 3 Day 1), and at the EOS visit.

Bone marrow aspirate (BMA) or biopsy samples were collected at screening for evaluation of disease, including samples for morphology and cytogenetics. A BMA or biopsy sample was subsequently collected to document a CR or nCR response or to assess suspected PD, if applicable.

**Safety Assessments:** The safety assessment was based on monitoring for adverse events (AEs) and serious AEs (SAEs), DLTs recorded during Cycle 1, symptom-directed physical examinations, vital signs, and clinical laboratory evaluations. Single electrocardiograms (ECGs) were collected at screening, with triplicate ECGs collected at prespecified times on Days 1, 15, and 16 in Cycle 1 only. A Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG Ntx) questionnaire was also completed by patients at the Screening visit and on Day 1 of every cycle.

**Statistical Methods:**

**Pharmacokinetic Analyses:** PK analyses were based on concentrations of MLN2238, the complete hydrolysis product of MLN9708 to the boronic acid. Mean MLN2238 concentration versus time plots were constructed using the individual patient concentration versus time data. PK parameters such as C$_{\text{max}}$, T$_{\text{max}}$, AUC$_{0-168}$, t$_{1/2}$, and accumulation ratio were determined for each patient, as permitted by the data, using noncompartmental analysis. Descriptive statistics for each parameter
were calculated for each MLN9708 dosing cohort. Dose-proportionality analysis was performed by assessing the relationship between AUC_{0-168} and actual dose (in mg) using a power model.

**Pharmacodynamic analyses:** Mean 20S proteasome inhibition versus time plots were derived using individual patient data. Pharmacodynamic parameters (E_{max}, first time of E_{max}, AUC_{0-168}) were determined for each patient using noncompartmental analysis. Descriptive statistics for each pharmacodynamic parameter were calculated for each MLN9708 dosing cohort as appropriate.

**Efficacy:** The efficacy analysis was based on the ORR (CR + PR) and CR + PR + MR rate. (Note stringent CR [sCR] is counted as CR, VGPR and nCR are counted as PR.) The number and percentage of patients in each of the disease response categories were descriptively tabulated for all patients. Time to response, duration of response, and other efficacy parameters were planned to be presented, as appropriate. Cytogenetic results were also described; high-risk cytogenetic results were defined as the presence of any of the following abnormalities: t(4;14), t(14;16), and del 17 (including loss of p53 gene).

**Safety:** AE incidence was tabulated for the following categories: all AEs, treatment-emergent AEs (TEAEs), most common TEAEs (those in ≥10% of patients), SAEs, drug-related TEAEs, Grade 3 or higher drug-related TEAEs, Grade 3 or higher TEAEs, TEAEs resulting in discontinuation of study drug, AEs resulting in dose reduction, and TEAEs resulting in dose modification. TEAEs were summarized by Medical Dictionary for Regulatory Activities version 15 preferred term. A by-patient listing of DLTs that occurred during Cycle 1 of treatment in patients enrolled in the dose escalation segment was also presented.

For hematology and chemistry parameters, shift tables were prepared for changes in the National Cancer Institute Common Terminology Criteria for Adverse Events from baseline to the worst post-baseline grade. Graphical displays were generated to show changes in clinical laboratory parameters, ECOG scores, and vital signs over time. ECG intervals (heart rate and corrected QT interval) were summarized at each scheduled time point, along with mean change from baseline to each post-treatment time point. A by-patient listing of the patient-reported FACT/GOG Ntx questionnaire 11-question subscale score was presented for each individual item at each time point. A summary table of total score was presented for all patients across time points. All concomitant medications collected from screening through the study period were classified to preferred terms according to the World Health Organization drug dictionary.

**RESULTS**

**Patient Disposition:** A total of 60 patients were enrolled, received at least 1 dose of MLN9708, and were included in the safety analysis of this study (32 patients in the dose escalation cohorts and 31 in the MTD expansion cohorts [note 3 patients from the MTD escalation cohort were combined into the MTD expansion cohorts for purposes of analysis]). The 32 patients enrolled in the dose escalation cohorts were as follows: 3 patients each were enrolled to receive 0.24 mg/m^2, 0.48 mg/m^2, 0.80 mg/m^2, and 1.20 mg/m^2; 4 patients were enrolled to receive 1.68 mg/m^2; 3 patients were enrolled to receive 2.23 mg/m^2; 8 patients were enrolled to receive 2.97 mg/m^2; and 5 patients were enrolled to receive 3.95 mg/m^2. The 31 patients enrolled to receive 2.97 mg/m^2 in the dose expansion cohorts were as follows. Of the 8 patients enrolled in the 2.97 mg/m^2 (MTD) escalation cohort, 2 were subsequently combined into the Relapsed and Refractory cohort, and 1 into the VELCADE-Relapsed cohort. In total, 11 patients were in the Relapsed and Refractory MTD expansion cohort, 10 were in the VELCADE-Relapsed MTD expansion cohort, 6 were in the PI-Naïve MTD expansion cohort, and 4 patients were in the Carfilzomib MTD expansion cohort.

The median duration of follow-up was 53.5 days (range, 1-324), which corresponds to the duration of treatment in this study. Of the 60 patients, 41 (68%) completed study treatment per protocol: specifically, 13 (22% of all 60 patients) received at least 4 cycles of treatment with MLN9708, and
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the remaining 28 (47%) experienced PD after completing at least 28 days of Cycle 1. The most common primary reason for discontinuation was PD (in 70% overall), followed by AE (12%), withdrawal of consent (10%), and unsatisfactory therapeutic response (2%).

**Baseline Characteristics:** Overall, 55% of patients were male, and the majority (85%) were white. The median age was 64.0 years. The median time since diagnosis was 58.6 months. A total of 41 (68%) patients had IgG myeloma, 10 (17%) had IgA myeloma, and the remaining 9 patients (15%) had light chain myeloma. The proportion of patients with an International Staging System (ISS) stage of I, II, and III disease was 30%, 48%, and 20%, respectively. Fifty-four patients (90%) had measurable disease at baseline, and most patients (67%) had lytic disease at baseline. The median β₂-microglobulin level was 3.80 mg/L, with 11 patients (18%) having a high level (> 5.5 mg/L) at baseline. Regarding albumin, 30 patients (50%) had levels < 3.5 g/dL at baseline. The median calculated creatinine clearance was 76.55 mL/min overall and was similar across the MTD expansion cohorts. Overall, 23% of patients entered the study with moderate or severe renal impairment (22% and 2%, respectively, with moderate defined as creatinine clearance 31-60 mL/min and severe, 21-30 mL/min). Cytogenetic data were available from 55 patients. Ten of the 50 patients with abnormalities (20%) had high-risk cytogenetics, of whom 6 had MM characterized as containing del 17.

The median number of lines of prior therapy received was 4.0 overall. The majority of patients in the safety population had received at least 3 lines of prior therapy (70%) before study entry and 28% had received ≥ 6 lines of prior therapy. Overall, 77% of patients previously had an autologous stem cell transplant.

A total of 42 patients (72%) were refractory to their last prior therapy: 11 patients (18%) were refractory to VELCADE, and 23 (38%) were refractory to lenalidomide or thalidomide, as last prior therapy. A total of 27 (68%) were refractory to VELCADE, and 3 patients (5%) were refractory to carfilzomib, in any line of prior therapy.

**Pharmacokinetic Results:** After oral administration, MLN2238 was rapidly absorbed with a median T_{\text{max}} of approximately 1 hour on both Day 1 and Day 15. At the MTD of 2.97 mg/m², the geometric mean (% coefficient of variation [CV]) Day 1 MLN2238 C_{\text{max}} (N = 24) and AUC_{0-168} (N = 17) were 69.8 (61) ng/mL and 906 (49) ng/mL * hr, respectively. The corresponding values after Day 15 dosing were 65.4 (61) ng/mL (N = 17) and 1710 (53) ng/mL * hr (N = 10). Dose proportionality was observed for MLN2238 Day 1 and Day 15 AUC_{0-168} within the dose range of 0.80 to 3.95 mg/m² (1.4 to 8.9 mg actual administered dose range) of MLN9708. The t_{1/2} ranged from 87.3 to 271 hours (3.6 to 11.3 days) after the Day 15 dose. The geometric mean (%CV) accumulation ratio based on AUC_{0-168} for all PK-evaluable patients was 2.03 (28), which is consistent with the once-weekly dosing regimen of MLN9708 and the observed t_{1/2} values.

**Pharmacodynamic Results:** Maximum inhibition of blood 20S proteasome activity was dose dependent. At the MTD of 2.97 mg/m², the mean (± standard deviation) E_{\text{max}} values on Day 1 and Day 15 were 62% (±22) and 68% (±22), respectively. Maximum 20S proteasome inhibition was observed shortly after MLN9708 administration on both Day 1 (median time to E_{\text{max}} of 1.5 hours) and Day 15 (median time to E_{\text{max}} of 1.1 hours), suggesting that the peak pharmacodynamic effect was directly related to the maximal MLN2238 plasma concentrations occurring after oral MLN9708 administration.

**Efficacy Results:** Measures of activity focused both on paraprotein reduction and investigator-assessed IMWG response criteria. Fifty patients were considered response evaluable: 23 in the dose escalation cohorts and 30 in the MTD expansion cohorts (3 patients from the dose escalation cohorts were combined into the MTD expansion cohorts). Response was assessed on the first day of every other cycle, beginning with Cycle 3.
In the 50 response-evaluable patients with at least 1 postbaseline M-protein measurement, 15 (30%) demonstrated a reduction in their paraprotein of at least 25%. Six of the 50 patients (12%) had a 25% to < 50% reduction in paraprotein level, with 9 (18%), 3 (6%), and 1 (2%) experiencing reductions of ≥ 50%, ≥ 90%, and 100%, respectively.

Five of the 15 patients with a reduction of at least 25% were known to be refractory to VELCADE at any line (defined as having PD while receiving VELCADE or within 60 days after the last dose of VELCADE as prior therapy). A reduction of at least 25% was seen in patients treated at 1.20 mg/m$^2$ and above and across MTD expansion cohorts. In 10 of these 15 patients, this paraprotein reduction qualified as a clinical objective response (unconfirmed or confirmed) of MR or better. M-protein reductions remained relatively stable over the course of treatment until PD.

On the basis of the investigator’s assessment, 10 patients had a confirmed (n = 7) or unconfirmed (n = 3) best response of MR, PR, or VGPR (in 1, 8, and 1 patient, respectively). All 10 were treated at or above the MTD. Therefore, the confirmed ORR (CR + PR) was 18% overall and 27% among all patients treated at the MTD. When including MR (CR + PR + MR), the ORR was 20% overall and was 9% and 13%, respectively, in the dose escalation and MTD expansion cohorts. Of these 10 patients, 7 (all with PR or better) had data available regarding whether or not their disease was VELCADE refractory. Two of the 7 (29%) were VELCADE refractory in any line, and 5 (71%) were not VELCADE refractory in any line (including 1 patient in the PI-naïve cohort).

In total, 27 patients were refractory to VELCADE at any line, of whom 2 achieved a PR or better, for an ORR of 7%. In addition, 1 of 11 patients refractory to VELCADE at last line achieved a PR (for an ORR of 9%), and 1 of the 3 carfilzomib-refractory patients had a PR (ORR, 33%). Five of the 27 VELCADE-refractory patients (19%) had an M-protein reduction of at least 25%; the reduction was ≥ 50% in 1 of the VELCADE-refractory patients (with a PR) and ≥ 90% in another (with a PR).

**Safety Results:** The MTD was established as 2.97 mg/m$^2$. The highest dose tested was 3.95 mg/m$^2$, and at this dose, 2 Cycle 1 DLTs were observed: 1 patient experienced Grade 3 vomiting, nausea, and diarrhea and 1 patient experienced Grade 3 erythema multiforme. In the 2.97 mg/m$^2$ (MTD) cohort, 1 patient experienced a Cycle 1 DLT of Grade 3 vomiting, diarrhea, and nausea.

In this dose escalation study, overall, all but 1 patient had a TEAE (98%); 85% had a drug-related TEAE. A total of 29 patients (48%) had at least 1 drug-related Grade 3 TEAE, and 11 (18%) had at least 1 drug-related Grade 4 TEAE. The most common TEAEs of any cause and any grade were fatigue (52%), thrombocytopenia (48%), diarrhea (45%), nausea (45%), and vomiting (40%). The most common drug-related TEAEs regardless of grade were thrombocytopenia (43%), diarrhea (38%), nausea (38%), fatigue (37%), and vomiting (35%). The most common Grade 3 drug-related TEAEs were thrombocytopenia (18%), diarrhea (17%), and neutropenia (17%). The only drug-related Grade 4 event reported in more than 1 patient was thrombocytopenia (9 patients [15%]). A total of 21 patients (35%) had an SAE, and 11 patients (18%) had a least 1 SAE that was considered to be related to study drug. All but 1 SAE occurred at or above the MTD. The most common treatment-related SAEs were diarrhea (5 patients [8%]), vomiting (3 [5%]), and nausea, pneumonia, and dehydration (in 2 patients each [3%]). All SAEs of vomiting and nausea were considered related to study drug. One on-study death was reported, and it was not considered by the investigator to be related to study drug.

Reported adverse events of clinical importance and special interest that were considered to be related to a study drug were further evaluated in detail. The highlights are as follows:

- Peripheral neuropathies not elsewhere classified (NEC) (peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy) were reported in 15 patients (25%): 9 (15%) with peripheral neuropathy, 5 (8%) with peripheral sensory neuropathy, and 2 (3%) with peripheral motor neuropathy (1 patient had both peripheral sensory and motor...
neuropathies). Of the 15, 6 had Grade 1 neuropathy, 8 had Grade 2, and 1 had Grade 3. None of the events were Grade 4 and none were SAEs. The neuropathy was considered drug related in 12 patients (20%). Thirteen of the 15 patients (87%) with a reported TEAE of peripheral neuropathy NEC had previously been treated with VELCADE, including 8 of the 9 patients who had a history of neuropathy at baseline and both patients with concurrent diabetes. Five of the 8 patients with Grade 2 peripheral neuropathy had Grade 1 neuropathy at baseline.

- Fourteen patients (23%) reported 25 events characterized as a rash. All rash events occurred at or above the MTD. The rash reported was presented with various clinical descriptions and was most commonly reported as macular rash, and appearing on the chest, abdomen, and back and occasionally on the neck, face, arms, hands, and thighs. The majority of the rash events were Grade 1 and 2 and were related to study drug. However, in 1 patient, the serious and potentially fatal skin condition of Stevens–Johnson syndrome/bullous erythema multiforme occurred, considered to be related to the study drug, but the event was completely resolved after a short course of systemic corticosteroids and other supportive care measures.

- Fifteen patients (25%) experienced a TEAE of anemia, 7 (12%) of whose events were Grade 3. Fourteen patients (23%) had at least 1 TEAE of neutropenia: 10 (17%) experienced Grade 3 neutropenia, and 1 (2%) experienced Grade 4 neutropenia (at 1 dose level above the MTD). This event of Grade 4 neutropenia was not associated with an infection and did not require hospitalization or antibiotics or growth factors. Only 1 patient received pegfilgrastim for neutropenia. Thrombocytopenia was a common TEAE, with 29 patients (48%) having at least 1 event, the majority of which were related to study drug. Overall, regardless of causality, 12 patients (20%) had Grade 3 thrombocytopenia, and 11 (18%) had Grade 4 thrombocytopenia. Most cases of Grade 4 thrombocytopenia were transient and most (7 of 11 patients [75%]) did not require administration of platelets; transfusion was performed in 4 affected patients (25%).

- Nine patients overall (15%) had AEs in the renal and urinary disorders system organ class (SOC), and 4 patients overall (7%) had AEs related to renal function analyses (ie, the preferred term of blood creatinine increased) within the investigations SOC. These were related to study drug in 3 patients (5%). The elevated creatinine was Grade 2 in 2 patients and Grade 3 in 2 patients, with 1 of each related and 1 of each not related to study drug. Three patients (5%) had renal failure (both Grade 2; 1 related and 2 not related), and 2 (3%) had acute renal failure (both Grade 3, with 1 event related and 1 not related). In addition, 2 (3%) experienced hyperuricemia (Grade 4 related in 1 patient and Grade 1 not related in the other). One patient (2%) discontinued because of Grade 3 elevated creatinine, and another (2%) discontinued for Grade 2 renal failure.

- Five patients (8%) had a TEAE under the cardiac SOC. All were Grade 1 or Grade 2 events except a Grade 4, drug-related, congestive cardiac failure event reported in a patient in the VELCADE-Relapsed MTD expansion cohort who had multiple preexisting cardiac conditions prior to the start of the study drug.

- Forty-six patients (77%) experienced gastrointestinal AEs. Eleven (18%) had at least 1 Grade 3 gastrointestinal TEAE, in 10 of whom it was related to study drug: Grade 3 diarrhea in 10 patients (17%) patients, Grade 3 nausea in 4 patients (7%), and Grade 3 vomiting in 3 patients (5%). There were no Grade 4 or Grade 5 TEAEs in the gastrointestinal SOC.

- Seven patients (12%) in the safety population had treatment-emergent pneumonia (all at or above the MTD), and all were treated with antibiotics. Of these 7 patients, 4 (7%) had
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Grade 3 or Grade 4 pneumonia, all 4 considered SAEs because the patients were hospitalized. Two of these SAEs were related to study drug and 2 were considered not related. No patient discontinued study drug owing to pneumonia.

CONCLUSIONS: This was the second clinical study of the oral formulation of MLN9708 (ixazomib citrate), a small-molecule 20S proteasome inhibitor, and the first study of once-weekly dosing. MLN9708 is the citrate ester of the biologically active dipeptide boronic acid MLN2238 (ixazomib).

In this open-label, multicenter, phase 1, dose escalation study, MLN9708 was administered orally once weekly on Days 1, 8, and 15 of a 28-day cycle to adult patients with RRMM who had been treated with at least 1 line of therapy. The dose of 2.97 mg/m² was selected as the MTD.

MLN9708 was rapidly absorbed after oral administration. Dose-proportional increases in MLN2238 AUC₀₋₁₆₈ on Day 1 and Day 15 were observed within the dose range of 0.8-3.95 mg/m² (1.4 mg to 8.9 mg actual administered dose range) of MLN9708. The t½ of MLN2238 ranged from 3.6 to 11.3 days. Maximum inhibition of 20S proteasome activity was dose dependent and occurred shortly after MLN9708 administration. This suggests a close temporal association between maximum whole blood 20S proteasome inhibition and the maximum observed plasma concentrations of MLN2238.

Overall, it appears that MLN9708 has single agent clinical activity in the majority of evaluable patients with MM refractory to and/or relapsed after multiple prior lines of therapy. Activity was seen across varying degrees of exposure and responsiveness to various prior therapies, including VELCADE. However, larger studies with longer duration of treatment will be needed to confirm these preliminary data and further establish the efficacy profile of MLN9708 in this patient population. The most common TEAEs, both overall and specifically drug related, thrombocytopenia, diarrhea, nausea, vomiting, and fatigue. Less than one-quarter of all patients experienced a Grade 4 treatment-related TEAE, consisting almost entirely of Grade 4 thrombocytopenia. Most cases of Grade 4 thrombocytopenia were transient and most did not require administration of platelets. One patient discontinued study drug because of Grade 3 related thrombocytopenia. Thrombocytopenia, as well as peripheral neuropathy, gastrointestinal events, and rash are all events of clinical importance in patients receiving PIs such as MLN9708 and are monitorable and manageable with standard medical interventions.

Although 8 patients (13%) discontinued study drug because of TEAEs, no specific TEAE led to the discontinuation of more than 1 patient. One on-study death, not related to study drug, was reported. Less than one quarter of patients experienced a treatment-related SAE.

The emerging safety profile indicates that oral MLN9708 administered once weekly can lead to TEAEs that are generally manageable and reversible with dose reduction and standard supportive care. The types of TEAEs observed were generally expected on the basis of nonclinical studies with MLN2238 and clinical experience with the first-in-class boronic proteasome inhibitor, VELCADE.

Our understanding of this molecule will benefit from combining data across trials, as appropriate, to gain a more nuanced understanding of the safety profile and from planned randomized clinical trials. The findings of this clinical trial also demonstrate the single agent antimyeloma activity of MLN9708 given once weekly and support ongoing clinical development.

Date of Report: 10 January 2014

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