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Phase II Study of the combination of MLN 9708 with Lenalidomide as Maintenance Therapy post Autologous Stem Cell Transplant in Patients with Multiple Myeloma

Protocol History

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1. INTRODUCTION AND STUDY RATIONALE

1.1 Overview of the Disease

Management of Myeloma has changed significantly over the past 10 years. The use consolidation of induction therapy with autologous stem cell transplantation (ASCT) has become an important part of the therapeutic plan for transplant eligible patients with multiple myeloma [1-5] demonstrating improvements in responses and translated to PFS and OS benefits. Based on the findings of 6 international trials looking at ASCT, the ASCT regimen of melphalan 200 mg/m2 has become the standard of care.

Despite the clinical benefit with the use of ASCT, myeloma continues to remain incurable, and patients progress within 2-3 years of single ASCT.

Several strategies, have attempted to improve on the single autologous transplant, using either consolidation or maintenance therapy. Various consolidation strategies include use of a second autologous stem cell transplant or combination chemotherapy/

A second strategy uses chemotherapy either as a single agent bortezomib or combinations regimens including bortezomib/thalidomide/dexamethasone or bortezomib/ lenalidomide/ dexamethasone. An ongoing national intergroup trial is designed to answer the role of consolidation therapy and the best strategy.

The second strategy to improve outcomes post transplant have been the use of long term maintenance therapy. Initial trials evaluated the use of alpha-interferon, prednisone with no significant benefit in survival and significant toxicity.

Multiple trials have studied immunomodulatory therapy with thalidomide to improve progression free survival post ASCT. All of the trials showed improvement in progression free survival however only 3 showed benefit in overall survival. Subset analysis showed benefit limited to patients in a partial remission post transplant and no benefit for patients with high risk cytogenetics and patients in a deeper remission including complete remission. The use of thalidomide has been limited by development of toxicity with long term use including neuropathy, somnolence and fatigue.

A second generation Imid, lenalidomide has been developed with improved side effect profile with limited neuropathy and somnolence. Lenalidomide has been approved in the relapsed myeloma in combination with dexamethasone.

Two trials have evaluated the role of lenalidomide in the post- transplant setting as maintenance therapy, in the US as an intergroup effort led by the CALBG, and the IFM group (1, 2). Continuous low dose lenalidomide demonstrated similar results between both studies with significant benefit in progression free survival. There was an absolute18-20 month increase in PFS, with an increase from 22+ months to 40+ months . The CALBG trial more recently and importantly has demonstrated early overall survival benefit. The benefit in PFS with lenalidomide, has also present in patients with high risk

cytogenetics and patient in complete remission post ASCT, which was not seen with maintnenace thalidomide. The use of maintenance lenalidomide has been very well tolerated with minimal neuropathy. The major toxicity has been leucopenia with limited neutropenic fevers. The second emerging signal has been development of second primary malignancies with use of lenalidomide and additional followup and data is needed.
In congregate the significant clinical benefit with improvement in PFS, limited side effect profile has established lenalidomide as an important therapeutic option.

Proteaseome inhibition has been studied post transplant in a hybrid consolidation /maintenance model with predefined course of bortezomib based therapy, which was well tolerated and led to significant improvement in response rates and benefit in PFS. However long term proteasome inhibitor therapy has been limited by the necessary IV administration.

The combination of proteasome inhibitors and immunomodulatory agents have strong preclinical rationale which have been confirmed with high response rates with all combinations of PI+IMid in both newly diagnosed and relapsed/refractory myeloma.

MLN9708 offers an exciting new opportunity as an active proteasome inhibitor with oral administration of therapy to be studied in the maintenance therapy. Multiple ongoing studies of MLN9708 as single agent and in combination with lenalidomide therapies are onging.

New treatment strategies to continue to improve progression free survival with maintenance therapy in an important window of opportunity to improve survival in patients with myeloma. We propose the addition of MLN9708 to lenalidomide as maintenance therapy will be a well tolerated regimen and lead to significant improvement in duration of remission post- transplant.

1.2 MLN9708

1.2.1 Scientific Background

1.2.2 Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management AttacNonclinical Pharmacology

Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.2.3 Nonclinical Pharmacokinetics and Pharmacodynamics

Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.2.4 Safety Pharmacology

Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.2.5 Toxicology

Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.2.6 Clinical Experience

As of 12 October 2011, 247 patients have been treated with MLN9708 across 7 enrolling, sponsor-led phase 1 or phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. Ongoing and planned studies include:

- Study C16001: phase 1, single-agent intravenous (IV) administration twice weekly in adult patients with advanced nonhematologic malignancies; N = 111
- Study C16002: phase 1, single-agent IV administration weekly in adult patients with advanced lymphoma; N = 21
- Studies C16003 and C16004: phase 1, single-agent oral (PO) administration twice weekly and weekly, respectively, in adult patients with relapsed or refractory MM (RRMM) (previous exposure to bortezomib, IMiD, and corticosteroid required); N = 56 and 32, respectively
- Study C16005: phase 1/2, PO administration weekly in combination with lenalidomide and low-dose dexamethasone every 28 days in adult patients with previously untreated transplant eligible MM; N = 15
- Study C16006: phase 1/2, PO administration twice weekly and weekly in combination with melphalan and prednisone (MP) in patients with previously untreated transplant ineligible MM; N = 6
- Study C16007: phase 1, single-agent PO administration weekly in patients with relapsed or refractory light-chain amyloidosis; N = 6

In addition to the trials noted above, there are currently 4 planned trials, each of which will use the PO formulation of MLN9708. These studies include:

- Study C16008: PO twice-weekly administration in combination with lenalidomide and low-dose dexamethasone every 21 days in adult patients with newly diagnosed multiple myeloma (NDMM)

- Study C16009: PO administration on Days 1 and 15 of the first 28-day cycle to assess drug-drug interactions (DDIs) with ketoconazole, relative bioavailability, and food effect in patients with advanced solid tumor malignances, lymphoma, or Waldenström's macroglobulinemia; in subsequent cycles, PO administration on Days 1, 8, and 15

Both Study C16008 and Study C16009 are in the process of institutional review board (IRB) and independent ethics committee (IEC) reviews and have not yet begun to enroll patients (for additional information, please refer to ClinicalTrials.gov).

The 2 planned phase 3 trials are:

- Study C16010: phase 3 trial of lenalidomide and dexamethasone with MLN9708 or placebo given weekly in patients with relapsed or refractory MM; currently in the development stage

- Study C16011: phase 3 trial of dexamethasone with MLN9708 given weekly versus physician's choice from a preselected list of available therapy in patients with relapsed or refractory AL amyloidosis; currently in the development stage

1.2.6.1 Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to first maximum plasma concentration (T_{max}) of approximately 0.5 to 2.0 hours and terminal $t_{1/2}$ after multiple dosing of approximately 5 to 7 days.[1] Results of a population PK analysis (N = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[2] Based on these data, a recommendation was made for fixed dosing in clinical

trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. See the IB for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

1.2.6.2 Clinical Trial Experience Using the Oral Formulation of MLN9708

As of 12 October 2011, a total of 115 patients have been treated with escalating doses of MLN9708 in 5 enrolling studies designed to investigate PO MLN9708 in patients with MM and amyloidosis. These studies are outlined in Table 1-1.

Table 1-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 56	PO, twice weekly (TW), single agent	0.24-2.23 mg/m^2, TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia
C16004 RRMM N = 32	PO, weekly (W), single agent	0.24-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting
C16005 NDMM N = 15	PO, W, combination with LenDex	1.68-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D*: 4.0 mg fixed (switch to fixed dosing in phase 2)
C16006 NDMM N = 6	PO, TW (Arm A) and W (Arm B), combination with melphalan and prednisone	Arm A*: 3-3.7 mg, fixed dose, TW Arm B*: 3-4.0 mg, fixed dose, W
C16007 RR-AL N = 6	PO, W, single agent	4-5.5 mg, fixed dose*, W

Abbreviations: AL = Primary systemic light chain (AL) amyloidosis ; DLT = dose-limiting toxicity; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RRAL = relapsed refractory amyloidosis; RRMM = relapsed and/or refractory multiple myeloma.

* Approximate body surface area (BSA) and fixed dosing equivalence: 3 mg ~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg ~ equivalent to 2.97 mg/m^2 BSA dosing.

The emerging clinical safety profile pooled from the ongoing trials indicates that PO MLN9708 is generally well tolerated with manageable, reversible, dose-dependent treatment emergent adverse events (TEAEs) that are consistent with class-based effects of proteasome inhibition though frequencies differ. As of 12 October 2011, the most frequent (> 10%) TEAEs irrespective of causality to PO MLN9708 (pooled data) are listed in Table 1-2.

Table 1-2 Oral MLN9708 Potential Risks Irrespective of Causality 12 October 2011 (N = 115)

Adverse Drug Reactions	**Fatigue (53%)** **Thrombocytopenia (36%)** **Skin rash (all terms) (36%)** **Nausea (35%), diarrhea (34%), vomiting (30%)**
Potential Risks Reported (> 10%) Due to MLN9708 or Disease Under Study	**Anemia (24%), neutropenia (17%)** **Anorexia (17%), fever (17%)** **Peripheral neuropathy (16%)** **Upper respiratory infection (15%)** **Cough (15%), arthralgias (15%)** **Dizziness (14%)** **Constipation (13%), headache (13%)** **Dehydration (10%), shortness of breath (10%)** **Abdominal (10%) or back pain (10%)** **Peripheral edema (10%)**

1.2.6.3 Relapsed and/or Refractory Multiple Myeloma

As of 12 October 2011, there are 2 ongoing, phase 1 clinical trials investigating PO MLN9708 in RRMM. In Study C16003 of twice-weekly MLN9708 (21-day cycle, Days 1, 4, 8, and 11), the MTD is 2.0 mg/m^2. In Study C16004 of weekly MLN9708 (28-day cycle, Days 1, 8, and 15), the MTD is 2.97 mg/m^2. In both trials, patients are enrolled into the following defined expansion cohorts: RRMM, bortezomib relapsed, proteasome inhibitor naïve, and carfilzomib exposed. Study C16003 (single agent, twice weekly) has completed accrual and Study C16004 (single agent, weekly) is enrolling patients into the expansion cohorts.

Study C16003: Single-agent, Twice-Weekly MLN9708

Study C16003 has enrolled 56 patients with the following characteristics: median age of 65.5 years (range 50–86); median time since initial MM diagnosis of 4.7 years (range 1.1-24.3); median number of prior therapies of 4 (range 1–28); 57% of patients had received stem cell transplant; 88%, 79%, 59%, and 4% had prior therapy with bortezomib, lenalidomide, thalidomide, and carfilzomib, respectively; and 52% were refractory to last therapy, including 28% who were bortezomib-refractory. Patients have received a median of 3.5 cycles of therapy (range 1-23+). Six patients have achieved at least a partial response (PR) (1 very good partial response [VGPR] and 5 PRs); additionally, 1 patient has achieved

a minor response (MR), and 28 patients have achieved durable disease stabilization for up to 12.9 months.[3]

In Study C16003, 1 of 3 patients experienced a protocol-defined dose-limiting toxicity (DLT) (Grade 3 rash) at a dose of 2.23 mg/m^2. Another patient at this dose experienced Grade 4 thrombocytopenia (platelet count of 10,000/mm^3). Per protocol, a DLT related to platelets required either a platelet count < 10,000/mm^3 or Grade 4 thrombocytopenia lasting more than 7 consecutive days; therefore, a platelet count equal to 10,000/mm^3 did not formally meet the protocol definition for DLT. Although thrombocytopenia and rash have been identified as adverse drug reactions (see the IB), both events have predictable patterns, are reversible (spontaneously or with standard medical treatment), and can be monitored in the clinic with routine clinical observations and tests. Therefore, after a discussion with the participating investigators, an intermediate yet lower dose was allowed in the C16003 protocol and supported by available PK data to further characterize dose-related toxicities. Six patients were treated at the intermediate dose of 2.0 mg/m^2, a dose approximately half way between the 2 existing dose levels of 2.23 mg/m^2 and 1.68 mg/m^2 (a dose without any DLTs). Given that not 1 patient (0/6) has experienced a DLT, the MTD of MLN9708 administered PO, twice weekly was determined to be 2.0 mg/m^2.[3]

A summary of the safety profile of patients treated in Study C16003 is outlined in Table 1-3. Overall, 98% of patients experienced a TEAE of any grade and of any cause.

Table 1-3 Study C16003, Twice–Weekly, Single–agent, Oral MLN9708: Most Common Treatment-Emergent Adverse Events as of 12 October 2011 (N= 56)

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (57%) Skin rash (all terms) (50%) Thrombocytopenia (41%) Nausea (34%), diarrhea (36%) Vomiting and fever (30% each) Cough (25%) Anorexia (23%) Neutropenia (21%)
Drug-Related Peripheral Neuropathy (PN) (n = 6)	4 patients with worsening to Grade 1 2 patients with worsening to Grade 2 All 6 had baseline Grade 1 PN at study entry
Drug-Related Grade ≥ 3 in more than 2 Patients (Overall 34 patients with at least 1 drug-related Grade 3 or higher adverse event)	Thrombocytopenia (n = 19) Neutropenia (n = 8) Fatigue (n = 5) Rash (all terms) (n = 5) Abdominal pain, anemia, hypophosphatemia, and leucopenia (n = 2 each)

Fifteen patients have experienced drug-related serious adverse events (SAEs) involving the following events: thrombocytopenia; anemia; neutropenia; febrile neutropenia; nausea; vomiting; abdominal pain; chest pain (noncardiac); orthostatic hypotension, hypotension, or hypophosphatemia; hyperuricemia; febrile neutropenia; fever; chills; rash, pneumonia; hypoxia; pulmonary hypertension; fall; headache; fatigue; and dehydration. Five patients discontinued therapy due to TEAEs (thrombocytopenia, pulmonary hypertension, and pruritic rash) that were considered at least possibly related to MLN9708, and spinal cord compression and bone pain, both considered related to disease progression. The 2 on-study deaths reported were not related to study drug.[3]

Study C16004: Single-agent, Weekly MLN9708

In Study C16004, where MLN9708 is administered weekly, 28 patients have been enrolled to the dose-escalation phase as of 12 October 2011. Patient characteristics included median age of 64 years (range 40–76), median time since initial MM diagnosis of 4.9 years (range 1.5–18.8), and median number of prior therapies of 6 (range 2–14); 72% of patients had received SCT; 97%, 91%, 56%, and 6% had prior bortezomib, lenalidomide, thalidomide, and carfilzomib, respectively; and 56% were refractory to last therapy, including 28% refractory to bortezomib and 41% refractory to lenalidomide-thalidomide. Patients have

received a median of 2 cycles of therapy (range 1-11+). Two patients in the dose-escalation phase have achieved an objective response: 1 achieved a VGPR (relapsed after 4 prior lines of therapy including SCT, thalidomide, bortezomib, lenalidomide, and carfilzomib); and 1 achieved a PR (relapsed after 4 prior lines of therapy including SCT, thalidomide, lenalidomide, perifosine, and bortezomib) . Additionally, 6 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 2 patients remain on treatment; discontinuation has been due mainly to progressive disease (69%).[4]

In Study C16004, 2 of 3 patients experienced a protocol-defined DLT (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m^2. Per the protocol, subsequent patients were treated at 1 dose level below (2.97 mg/m^2) where 1 of 6 patients experienced a protocol-defined DLT (Grade 3 nausea, vomiting, and diarrhea). Based on this information and other safety data, the MTD of weekly PO MLN9708 was determined to be 2.97 mg/m^2. This dose cohort is currently being expanded to further evaluate the safety and activity of MLN9708.[4]

Table 1-4 provides a summary of the safety profile of patients treated in Study C16004. Overall, 97% of patients experienced a TEAE of any grade and of any cause.

Table 1-4 Study C16004, Weekly Single-agent Oral MLN9708: Most Common Treatment-Emergent Adverse Events as of 12 October 2011 (N = 32)

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (50%) Thrombocytopenia (34%) Nausea (38%), diarrhea (31%) Vomiting (28%)
Drug-Related Peripheral Neuropathy (PN) (n = 3)	1 patient with worsening to Grade 1 2 patients with worsening to Grade 2 All 3 events were baseline Grade 1 PN at study entry
Drug-Related Grade ≥ 3 in more than 2 Patients (Overall, there have been 8 patients with at least 1 drug-related Grade 3 or higher adverse event)	Thrombocytopenia (n = 4; 1 Grade 4 and 3 Grade 3) Neutropenia and diarrhea (n = 3 each) Nausea and Fatigue (n = 2 each) Anemia, dehydration, vomiting, dizziness, rash (erythema multiforme) (n = 1 each)

There have been 2 drug-related SAEs involving diarrhea, dehydration, and dizziness. Six patients discontinued therapy due to a TEAE (thrombocytopenia, rash, neutropenia, diarrhea, nausea, vomiting, and abdominal pain) that was considered at least possibly related to MLN9708. The 1 on-study death reported was determined to be related to disease progression.[4]

1.2.6.4 Newly Diagnosed Multiple Myeloma (NDMM)

Study C16005 has completed enrollment to the phase 1 portion of the study and is enrolling into the phase 2 portion. MLN9708 is given weekly on Days 1, 8, and 15 with lenalidomide on Days 1 through 21 and dexamethasone on Days 1, 8, 15, and 22 of a 28-day cycle. This study has enrolled 15 patients as of the clinical data cut (12 Oct 2011) to 4 dose cohorts. No DLTs were seen at doses up to 2.23 mg/m^2. Three of 3 patients treated at the 3.95 mg/m^2 dose cohort experienced Grade 3 nausea and vomiting despite adequate antiemetic therapy; 1 patient additionally experienced Grade 2 syncope, and, in another patient the dose of lenalidomide was compromised such that < 80% of the planned doses were received. Per the protocol, subsequent patients were treated at 1 dose level below (2.97 mg/m^2), at which 1 of 6 patients experienced a protocol-defined DLT (Grade 3 rash). The MTD of weekly MLN9708 in combination with a 28-day cycle of lenalidomide and dexamethasone was established at 2.97 mg/m^2. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial, which included, but were not limited to, analyses of efficacy results (response rates: complete response [CR] and VGPR) and toxicity characterization (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). For the purpose of the RP2D estimation, Cycle 1 data from 6 evaluable patients were used in addition to the available clinical data supporting tolerance over multiple treatment cycles. Based on this review, the RP2D dose was determined to be 2.23 mg/m^2 in this combination. The clinical development of MLN9708 included a population PK analysis evaluating the feasibility of switching from BSA-based dosing to fixed dosing.[2] The results of this analysis support this transition; therefore, in Study C16005, all patients treated in the phase 2 portion of the trial will receive PO MLN9708 at a dose of 4.0 mg (the RP2D dose of 2.23 mg/m^2 × the mean patient BSA of 1.86 m^2).[5]

As of 12 October 2011, patients in Study C16005 have completed a median of 5 cycles (range 1-9). To date, all 15 response-evaluable patients have achieved at least a PR to therapy, including 4 CRs, 4 VGPRs, and 7 PRs; 14/15 of patients achieved at least a PR by the end of Cycle 1, and all 15 achieved at least a PR after Cycle 2.[5]

Table 1-5 provides a summary of the safety profile of patients treated in Study C16005. Overall, 100% of patients experienced a TEAE of any grade and of any cause.

Table 1-5 Study C16005, Weekly Oral MLN9708 Administered in Combination With Lenalidomide and Dexamethasone: Most Common Treatment-Emergent Adverse Events as of 12 October 2011 (N = 15)

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (60%) Vomiting (53%) Anemia (40%) Diarrhea and nausea (33% each) Insomnia, peripheral edema, and thrombocytopenia (27% each)
Drug-Related Peripheral Neuropathy (PN) (n = 3)	2 patients developed Grade 1 PN
Drug-Related Grade ≥ 3 in ≥ 2 Patients (Overall, 8 patients with at least 1 drug-related Grade 3 or higher adverse event)	Rash and vomiting (n = 2 each)

Related means to ANY drug in the study drug combination.

There have been no on-study deaths. One patient has discontinued study drug due to a TEAE deemed unrelated to study drug. Four patients have experienced drug-related SAEs involving nausea, vomiting, dehydration, dizziness, fainting, orthostatic hypotension, hypotension, deep vein thrombosis (DVT), atrial fibrillation, and muscle weakness.[5]

An additional study is being conducted in patients with NDMM, Study C16006, "An Open-Label, Dose-Escalation, Phase 1/2 Study of the Oral Form of MLN9708, a Next-Generation Proteasome Inhibitor, Administered in Combination With a Standard Care Regimen of Melphalan and Prednisone in Patients With Newly Diagnosed Multiple Myeloma Requiring Systemic Treatment". In this study, PO MLN9708 is being administered on the twice-weekly schedule in 1 group and on the weekly schedule in a second group. This study recently started to enroll patients. As of 12 October 2011, 6 patients, 3 per treatment group, have been treated, and all patients have received a fixed starting dose of 3.0 mg with standard doses of melphalan and prednisone.

1.2.6.5 Clinical Trial Experience Using the Intravenous Formulation of MLN9708

See the IB for descriptions of the 2 ongoing studies investigating IV MLN9708 in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.2.6.6 Clinical Trial Safety Experience: Pooled Intravenous and Oral Formulation

The potential risks reported with MLN9708 use, pooled from the enrolling 7 phase 1 and phase 1/2 clinical studies (including both IV and PO formulations) are shown in Table 1-6. Although the predominant potential toxicities may be severe in some cases, they are largely

reversible and can be managed by routine clinical monitoring and standard medical interventions, which may include dose reduction or supportive care. There is also consistency in the type of TEAE reported regardless of the MLN9708 formulation, even though there are differences in the frequency and severity of the reported events. Over all, the weekly schedule is active and has milder toxicities than the twice-weekly schedule. The most frequent AEs, listed in Table 1-6, were anticipated based on nonclinical data and previous experience with bortezomib.

Table 1-6 MLN9708 Potential Risks (Pooled Intravenous and Oral Formulations) as of 12 October 2011

Adverse Drug Reactions	Thrombocytopenia Skin rash (Includes terms: erythematous, generalized, pruritic, macular, macula-papular, papular) Nausea, vomiting, diarrhea Fatigue
Potential Risks Reported (> 10%) Due to MLN9708 or Disease Under Study	Fever Anorexia, constipation, dehydration Anemia, neutropenia Headache Dizziness Upper Respiratory Infection, dyspnea, cough Chills Arthralgia Abdominal or back pain Peripheral edema

Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA) for more information.

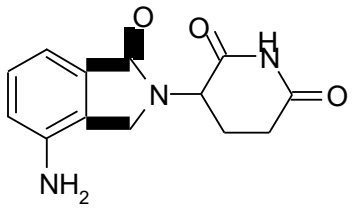
1.2.7 Potential Risks of MLN9708

Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.3 Lenalidomide (CC-5013)

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

REVLIMID® (lenalidomide) is available in 5 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

REVLIMID® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy. All other uses are considered investigational.

Clinical Pharmacokinetics and Pharmacodynamics

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and

4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

1.3.1 **Pharmacokinetic Parameters**

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

Supplier(s)

Revlimid® (lenalidomide) will be billed to the patients insurance through commercial supply to study participants.

Dosage form

Lenalidomide will be supplied as capsules for oral administration.

Packaging

. Bottles will contain a sufficient number of capsules for one cycle of dosing**.**

Storage

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Prescribing Information

Lenalidomide will be provided in accordance with the RevAssist® program. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of Celgene's RevAssist® program. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Special Populations:

Patients with Renal Insufficiency: The pharmacokinetics of lenalidomide in MDS patients with renal dysfunction has not been determined. In multiple myeloma patients, those with mild renal impairment had an AUC 56% greater than those with normal renal function. (See **PRECAUTIONS**: **Renal Impairment**).

Patients with Hepatic Disease: The pharmacokinetics of lenalidomide in patients with hepatic impairment has not been studied.

Age: The effects of age on the pharmacokinetics of lenalidomide have not been studied.

Pediatric: No pharmacokinetic data are available in patients below the age of 18 years.

Gender: The effects of gender on the pharmacokinetics of lenalidomide have not been studied.

Race: Pharmacokinetic differences due to race have not been studied.

1.3.2 **Deep Venous Thrombosis and Pulmonary Embolism**

This drug has demonstrated a significantly increased risk of DVT and PE in patients with multiple myeloma who were treated with REVLIMID® (lenalidomide) combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling

OTHER ADVERSE EVENTS

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulites, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

1.3.3 **INDICATIONS AND USAGE:**

Revlimid® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

1.3.4 **Clinical Experience**

A Phase I study in subjects with refractory or relapsed MM was conducted to identify the maximum tolerated dose (MTD) and to evaluate the safety of lenalidomide given orally for up to 4 weeks at 5 mg/day, 10 mg/day, 25 mg/day and 50 mg/day. Secondary objectives included evaluation of response to lenalidomide, as well as pharmacokinetics and identification of surrogate markers to aid in defining mechanisms of action. Subjects who tolerated study drug with acceptable toxicity and were without disease progression were permitted to continue on therapy beyond 28 days as part of an extension phase for over 1 year. Twenty-seven subjects were enrolled, of whom 15 had undergone prior autologous stem cell transplantation and 16 had received prior thalidomide, with a median of 3 prior regimens (range 2-6). All subjects had relapsed MM and 18 (72%) were refractory to salvage therapy. Two subjects were removed from study on the first day of treatment due to rapid disease progression, which resulted in renal dysfunction and rendered them ineligible. The first group of 3 subjects were treated for 28 d at 5 mg/d without any dose limiting toxicity (DLT). The second cohort of 3 subjects commenced therapy at 10 mg/day. In one subject, DLT was encountered with grade (G) 2 fever as well as G3 leukopenia and neutropenia, resulting in removal from study before day 28. Two subjects tolerated drug. Three additional subjects were treated at 10 mg/day with no attributable toxicity within the first 28 days. In the third cohort of 3 subjects at 25mg/day, drug was well tolerated within the first 28 days but G3 thrombocytopenia and G3 and G4 neutropenia occurred during the second month, resulting in 2 subjects being removed from study. In the fourth cohort at 50mg/day, the first 3 subjects tolerated treatment without DLT in the first 28 days and a subsequent 10 subjects also tolerated drug without DLT within the first 28 days. However, subsequent G3 thrombocytopenia and G3/4 neutropenia in the extension phase has prompted dose reduction and GCSF support in all subjects. No significant somnolence, constipation or neuropathy has been seen in any cohort. Median duration of therapy is currently 4 months [range 2 weeks – 14 months] and 11 subjects continue on treatment. Maximal protein reductions seen during therapy in subjects who have received $\geq$ 28d of treatment are summarized below:

Table 1-2 M Protein Reductions in a Phase I Study with Lenalidomide

Dose [mg]	Pts [n]	< 25%	$\geq$ 25% <50%	>50%	Progression

5	3	-	2	1	-
10	5	-	-	1	4
25	3	1	2	-	-
50	13	3	5	4	1
Subtotals	24	4 (17%)	9 (37%)	6 (25%)	5 (21%)

Thus, best responses in protein of $\geq$ 25% have been seen in 15 of 24 evaluable pts (63%), and a <25% reduction has been seen in 4 subjects to achieve stable disease or better in 19 of 24 (79%). Pharmacokinetics [days 1-4, and 28] have been completed in 24 subjects and reveal rapid absorption (t max: 1-1.5 h); monophasic elimination (t ½: 3.1-4.2 h), and low to moderate inter-subject variability for AUC (11-52%) and C max (3-33%). Furthermore, there was no significant accumulation by day 28. In conclusion, these studies suggest Lenalidomide at the dose levels studied has anti-tumor activity, continuous pharmacokinetics (PK) with convenient daily oral dosing and acceptable toxicity in subjects with relapsed and refractory multiple myeloma. (Richardson et al.,2002)

Given the myelosuppression beyond day 28 seen in all subjects at 50 mg/day, this dose was considered to be the DLT, and thus the 25 mg/day dose level as a continuous daily schedule of administration was considered MTD. Given the activity of the drug seen at lower dose levels and the PK characteristics observed, 30 mg/day in divided or single daily dose was assessed for activity and safety, and to determine whether a divided dose schedule is superior. In addition, a 3-week on and one-week off schedule was assessed to determine if a cycling schedule would decrease the myelosuppression that was observed in earlier trials with daily dosing. In this phase II study, 70 subjects with relapsed and refractory Myeloma were enrolled at several centers in the U.S. Richardson et al reported that 26% of subjects required dose reduction due to myelosuppression in this study. Responses that were observed included 4% of subjects with complete responses, 17% with partial responses and 33% with minimal responses. Progressive disease occurred in 15% of subjects (Richardson et al., 2002). It was concluded that daily dosing was better tolerated than twice daily dosing because of a lower incidence and severity of myelosuppression.

Data from two phase III trials comparing lenalidomide + dexamethasone to single agent dexamethasone in patients with relapsed and/or refractory multiple myeloma were presented at the 10th International Multiple Myeloma Workshop in Sydney Australia (Weber et al., 2005; Dimopoulos et al., 2005). Patients who had received 1-3 prior therapies, and progressing on their last therapy were randomized to receive lenalidomide, 25 mg/d x 21 d, placebo d22-28 plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, q 28d or placebo daily x 28 d plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, q28d. The responses reported are summarized in Table 1-4 while the incidence of DVT and pulmonary embolism are summarized in Table 1-5. Anemia, thrombocytopenia, neutropenia, fatigue, neuropathy, and constipation were also observed more often in lenalidomide + dexamethasone group compared to dexamethasone only group, however these events were generally manageable.

Table 1-3 Response Rates in Phase III Trials of Relapse refractory MM (Celgene MM-009 and MM-010)

	Weber et al (ASCO 05 oral presentation)			**Dimopoulos et al (ASH 2005 # 6)**		
	Lenalidomide + Dexa (n=170)	**Dexa Alone (n=171)**	***P* Value**	**Lenalidomide + Dexa (n=176)**	**Dexa Alone (n=175)**	***P* Value**
Overall Response Rate (%)	61%	23%	≤0.001	59%	24%	≤0.001
TTP (mo.)	15	5	≤0.00001	11.3	4.7	≤0.00001

Table 1-4 DVT & PE Risks in Phase III Trials of Relapse refractory MM (Celgene MM-009 and MM-010)

	Weber et al*		**Dimopoulos et al***	
	Lenalidomide + Dexa	**Dexa Alone**	**Lenalidomide + Dexa**	**Dexa Alone**

Deep Vein Thrombosis (%)	13.5	3.5	5.0	5.0
Pulmonary Embolism (%)	2.9	0.6	4.0	1.0

Oral presentation from Dimopoulos ASH 2005

1.4 Study Rationale and Selection of Drug Doses

There have significant advances in the management of multiple both in the relapsed/refractory, newly diagnosed patients with subsequent improvements in response rates, and survival. The role of maintenance therapy and the optimal regimen post autologous stem cell transplant (ASCT) in the myeloma paradigm continues to evolve.

Both lenalidomide and bortezomib have been evaluated as maintenance therapy post ASCT.

CALBG 100104 was a phase III trial which randomized patients post ASCT to maintenance lenalidomide 10 mg/day or placebo. Maintenance lenalidomide on an intention to treat analysis lead to a 20.5 month improvement in time to progression (TTP) from 21.8 months to 42.3 months with 17 months of followup. This benefit in TTP was seen in patients with prior thalidomide or lenalidomide based induction therapies. The major toxicity was hematologic toxicity, with 43% of patients experiencing grade 3/4 neutropenia, 13% with G3/4 thrombocytopenia with 12% patients discontinuing therapy due to any adverse event.

A second trial, IFM 2005-02 trial randomized patients post ASCT to placebo or 2 months of consolidation with lenalidomide 25 mg/day for days 1-21 for 2 months followed maintenance lenalidomide 10-15 mg daily. This led to an improvement in progression free survival post transplant from 24 months to 42 months.

These two trials have established maintenance lenalidomide as an important therapeutic option leading to significant improvements in PFS and potentially overall survival.

The combination of proteasome inhibitors and lenalidomide have been studied preclincally demonstrating synergy and clinically in both induction therapy as well as relapsed myeloma with promising activity.

The combination also warrant further exploration as the maintenance therapy post transplant. Specifically the addition of oral MLN 9708 to lenalidomide, is attractive as an all oral regimen with expected improvements in PFS/TTP compared to single agent lenalidomide.

The dosage of lenalidomide will be based on the CALBG experience with 10 mg and modified as tolerated. The dose of MLN 9708 will be based on the single agent experience as well combination studies. We will start 3 mg orally on day 1, 8, and 15 and dose modifications based on tolerability.

2. STUDY OBJECTIVES

2.1 Primary Objective

- Establish safety and efficacy of oral MLN 9708 and lenalidomide in the maintenance setting post ASCT in myeloma patients
- Primary endpoint:
  - Progression free survival (PFS)

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Incidence of secondary primary malignancy
- Evaluate the best response rate (sCR/nCR/VGPR/PR)
- Evaluate time to progression
- Evaluate time to next therapy
- Evaluate the tolerability and toxicity
- Evaluate MDASI- Myeloma symptom evaluation.

3. INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

Eligible patients will be enrolled and maintenance therapy on protocol no less than 60 days and must be initiated no more the 180 days post ASCT.

Patients will have standard restaging studies prior to initiation of therapy.

Standard post transplant therapy per institutional guidelines will be unaltered including prophylaxis therapy, vaccinations and restaging.

Patients who have completed ASCT and meet eligibility criteria will initiate maintenance therapy based on time on enrollment either in the phase dose escalation or expansion portion of trial.

Patients' clinical laboratory values and toxicity must be as specified below within 5 days before the first dose of study drug:

- Platelet count $\geq 100{,}000/mm^3$
- Neutrophil count $\geq 1000/mm^3$ (No growth factors within 5 days)
- Total bilirubin $\leq 1.5 \times$ ULN
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN
- Creatinine < 2.5 mg/dL

Recovered (ie, $\leq$ Grade 1 toxicity) from the reversible effects of autologous stem cell transplant.

Each cycle will be defined as a 28 day cycle. Drug holidays and break in therapy including those due to holidays, physician discretion and drug delivery are allowed as needed. Study drug will begin at Lenalidomide (10 mg/day); after three cycles , provided the ANC is ≥ 1000/µL, platelet count ≥ 100,000/µL, and all nonhematologic toxicity is ≤ grade 1, then the dose may be increased to 15 mg/day at discretion of physician.

MLN 9708 will be dosed at 3 mg flat dose on days 1, 8, 15 administered orally.

Patients will be allowed to receive radiotherapy for palliation of symptoms during the course of maintenance therapy

Study visits and procedures are detailed in the study table in the Appendix.

3.2 Selection of Patients

The total number of patients to be treated in this study is up to 64 patients (48 total patients dosed at 3 mg).

3.2.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1.Patient must have undergone autologous stem cell transplantation, with melphalan as a preparative regimen, within 12 months of initiation of induction therapy for newly diagnosed myeloma.

2. Time to initiation of maintenance therapy.

Patients may start maintenance therapy as early as 60 days post transplant and up to -180 post transplant; as long as they meet the following criteria:

- Platelet count ≥ 100,000/mm^3
- Neutrophil count ≥ 1000/mm^3. (No growth factors within 5 days)
- Total bilirubin ≤ 1.5 × ULN
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN
- Creatinine < 2.5 mg/dL
- Recovered (ie, ≤ Grade 1 toxicity) from the reversible effects of autologous

stem cell transplant.

3. Patients whose primary therapy was changed due to suboptimal response of toxicity will be eligible, however no more than 2 regimens will be allowed prior to ASCT.

4. Male or female patients 18 years or older.

5. Patients must have an Eastern Cooperative Oncology Group (ECOG) status of 0 to 2.

6. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

7. Female patients who:

- Are postmenopausal for at least 1 year before the Screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent, during study treatment and for 28 days after the last dose of study treatment, OR agree to completely abstain from heterosexual intercourse

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 28 days after the last dose of study treatment, OR
- Agree to completely abstain from heterosexual intercourse

3.2.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Patient has ≥ Grade 2 peripheral neuropathy.
2. Major surgery within 14 days before the first dose of study drug.

3. Radiotherapy within 14 days before enrollment

4. Known active central nervous system involvement

5. Systemic treatment, within 14 days before study enrollment, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort

6. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or GI procedure that could interfere with the oral absorption or tolerance of treatment.

7. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

8. Female subject is pregnant or lactating.

9. Serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with participation or completion of treatment according to this protocol.

10. QTc B> 470 milliseconds (msec) on a 12-lead ECG obtained during the Screening period. If a machine reading is above this value, the ECG should be reviewed by a qualified reader and confirmed on a subsequent ECG.

11. Ongoing or active systemic infection, known human immunodeficiency virus (HIV) positive, known active hepatitis B virus hepatitis, or known active hepatitis C virus hepatitis.

12. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

13. Known allergy to any of the study medications, their analogues, or excipients in the various formulations.

14. Participation in clinical trials with other investigational agents not included in this trial, within 21 days of the start of this trial and throughout the duration of this trial.

15. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the effects of prior chemotherapy regardless of the interval since last treatment.

16. Co-morbid systemic illnesses or other severe concurrent disease that, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.3 Study Treatments

3.3.1 Clinical Trial Materials

MLN9708

MLN9708 will be provided by Millenium at no cost.

Lenalidomide (REVLIMID®)

Lenalidomide (REVLIMID®) is commercially available oral drug supplied in 25mg, 10mg and 5mg capsules.

3.3.2 Preparation, Handling, Storage, and Destruction of Drugs

Drug Administration

Lenalidomide (Revlimid®) Administration:

For study participants, commercial supply of lenalidomide will be utilized and administered through the RevAssist® program.

Women of childbearing potential should not handle or administer the clinical dosage forms unless they are wearing gloves.

Only enough lenalidomide for 1 cycle may be provided to the patient each cycle.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Accurate records will be kept in the source documents of all drug administration (including prescribing and dosing).

Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary.

MLN9708

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Patients should be monitored for toxicity, as necessary, and doses of MLN9708 should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of MLN9708 dose (see Section 3.3.3) and per PI discretion.

MLN9708 Administration

Capsules of MLN9708 will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 0.2, 0.5, and 2.0 mg MLN9708.

The prescribed administration of MLN9708 doses in this study is 3 mg MLN9708 on days 1, 8, 15 on a 28 day cycle.

Patients should be instructed to swallow MLN9708 capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

MLN9708 Destruction

Investigational MLN9708 (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

3.3.3 Dose Modification and Delay

Before each cycle the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov/reporting/ctc.html). Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. If multiple toxicities are noted, the dose adjustments and/or delays for lenalidomide and MLN9708 are per PI discretion and suggest refer to guidelines that address the most severe toxicity.

3.3.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with Lenalidomide and MLN9708 will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm3.
- Platelet count must be ≥ 75,000/mm3.

In addition, all other toxicity considered to be related to treatment with MLN9708 must have resolved to ≤ Grade 1, to the patient's baseline values, or to a level considered acceptable by the physician (eg, hypokalemia that can be managed by replacements) before a new cycle of MLN 9708 treatment may begin.

If greater than > 4 week delay in starting subusequent cycle due to recovery from toxicity, consider dose reduction in attributable drug.

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed until recovery. The maximum delay before treatment should be discontinued will be 6 weeks or at the discretion of the Principal Investigator.

Intracyle dosing :

Lenalidomide should be held if plt < **If platelet count ≤ 30 × 10^9/L or ANC ≤ 0.75 × 10^9/L**
If platelet count ≤ 30 × 10^9/L or ANC ≤ 0.75 × 10^9/L until recovered to platelet > 75,000 and ANC > 1.0

Suggested Dose Modification patients if on Lenalidomide 10 mg

	Lenalidomide	MLN 9708
Dose -1	unchanged	2.4 mg
Dose -2	10 mg q 21	2.4 mg
Dose -3	10 mg q 21	1.5 mg
Dose -4	5 mg q 21	1.5 mg

Suggested Dose Modification If on lenalidomide 15 mg

After 3 cycle is if the Lenalidomide has been increased to 15 mg daily use the following dose modification:

	Lenalidomide	MLN 9708
Dose – 1	10 mg q 28	3mg
Dose -2	10 mg q 28	2.4mg
Dose -3	10 mg q 21	2.4mg
Dose -4	10 mg po q 21	1.5mg
Dose -5	5 mg q 21	1.5mg

For dosing recommendations upon recovery, refer to Table 3-2 and Table 3-3.

Table 3-1 Dose Reduction Steps for MLN9708

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
3.0 mg	2.4mg	1.5mg	Discontinue MLN9708

3.3.4 Dose Adjustments for Hematologic Toxicity

MLN9708 Dose Adjustments for Hematologic Toxicity

Dosage adjustments for hematologic toxicity are outlined in Table 3-2.

Table 3-2 MLN9708 Dose Adjustments for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• **If platelet count ≤ 30 × 10^9/L or ANC ≤ 0.75 × 10^9/L on a MLN9708 dosing day (other than Day 1)**	• **MLN9708 dose should be withheld.** • **Complete blood count (CBC) with differential should be repeated as clinically indicated** • **Upon recovery, MLN9708 may be reinitiated with 1 dose level reduction.**
•	•
Dose Modifications for Subsequent Treatment Cycles	
• **All hematologic toxicities**	• **For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle,:** ○ **If dose was reduced within the cycle, start the next cycle at that same dose.** ○ **If due to toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce MLN9708 by 1 dose level at the start of that cycle.** ○ **Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.**

3.3.5 Treatment Modifications for MLN9708-related AEs (Non-Hematologic Toxicities)

Treatment modifications due to MLN9708-related AEs are outlined in Table 3-3.

Table 3-3 MLN9708 Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only[6]
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold study drug until resolution to Grade ≤ 1 or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)[6]
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated[6]
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 3 nonhematologic toxicity judged to be related to study drug	• Hold study drug until resolution to Grade < 1 or baseline	Symptomatic recommendations noted in Section 3.4
If not recovered to < Grade 1 or baseline within 4 weeks	• Reduce study drug 1 to next lower dose upon return to < Grade 1 or baseline	
Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 4 weeks	• Hold study drug until resolution to Grade < 1 or baseline • Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 nonhematologic toxicities judged to be related to study drug	• Ppermanently discontinuing study drug	

Once MLN9708 is reduced for any toxicity, the dose may not be re-escalated

3.3.5 Packaging and Labeling

MLN9708

For blistered material, the capsules are packaged in cold form foil-foil blisters with a paper backing for child-resistance.

MLN9708 is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling MLN9708 capsules.

The study drug MLN9708 capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations. The formulation consists of 0.2-, 0.5-, and 2.0-mg capsules for oral administration.

MLN9708 capsules may be stored unopened at 2°C to 8°C (36°F-46°F). The capsules are individually packaged in cold form foil-foil blisters with a paper backing for child resistance. The capsules are in 1 × 4 blister strips that are individually perforated. The strips (1 × 4) are placed in cartons containing 6 strips (24 total capsules) of the same strength.

Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN9708 should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). All excursions should be brought to Millennium's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient 52in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister

packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because MLN9708 is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of MLN9708, including that MLN9708 is to be taken as intact capsules.

3.4 Management of Clinical Events

Prophylaxis Against Risk of Infection

If lymphopenia is noted, patients may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir or valacyclovir may be initiated as clinically indicated. Other antivirals are also acceptable.

Thromboembolism Prophylaxis

For patients at high risk, thromboprophylaxis according to ASCO guidelines or institutional standard of care is recommended.

Nausea and/or Vomiting

Standard anti-emetics, including 5-HT_3 antagonists, are recommended for emesis occurring upon treatment initiation; prophylactic anti-emetics may also be considered.

Dexamethasone should not be administered as an anti-emetic. Fluid deficits should be corrected before initiation of study drug and during treatment.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficits should be corrected before initiation of treatment and during treatment.

Erythematous Rash With or Without Pruritus

Rash has been reported with both lenalidomide and MLN9708. The lenalidomide-Induced rash is characterized as generalized, maculopapular, morbilliform, urticarial, papular, often with pruritus, and is noted as a warning/precaution in the lenalidomide package insert (PI). Serious skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported. Lenalidomide interruption Or discontinuation should be considered as described in the PI/Summary of Product Characteristics (SmPC).

As with VELCADE, rash with or without pruritus has been reported with MLN9708, primarily at the higher doses tested. The rash may range from some erythematous areas to macular and/or small papular bumps that may or may not be pruritic over a few areas of the body or more generalized, or it may have been transient and resolved either spontaneously or with standard symptomatic measures such as oral or topical antihistamines. Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone $\leq$ 10 mg per day or equivalent) is permitted.

Thrombocytopenia

Thrombocytopenia has been reported with both MLN9708 and lenalidomide. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. MLN9708 or lenalidomide administration should be modified as noted as per dose modification recommendations when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts.

Neutropenia

Neutropenia has been reported with both MLN9708 and lenalidomide. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable with G-CSF according to standard clinical practice. MLN9708 or lenalidomide administration should be modified when neutropenia occurs, as noted in the dose modification recommendations in Table 3-2. Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

Fluid Deficits

Dehydration should be avoided because lenalidomide is substantially excreted by kidney, and MLN9708 may cause vomiting, diarrhea, and dehydration. Two cases of acute renal failure have been reported in patients treated at or above the MTD with IV administration of MLN9708. There has been no treatment-related renal failure reported in patients treated with PO MLN9708. Fluid deficits should be corrected before initiation of study drug and during treatment. Until further information is available, intake of NSAIDs while on this protocol should be avoided.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including

considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

3.5 Concomitant Treatment

3.5.1 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care shall be available to patients as necessary.

The following are examples of those permitted during the study:

- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin).
- Patients may be transfused with red cells and platelets as clinically indicated.
- Prophylactic antibiotics for pneumocystis prophylaxis (such as Bactrim) is allowed.
- Antiviral therapy such as acyclovir is recommended for all patients.
- Concomitant treatment with bisphosphonates will be permitted.

- Patients who experience worsening neuropathy from baseline may be observed for recovery, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator. Dose reduction is suggested, when and if the patient resumes MLN9708 therapy.

3.5.2 Prohibited Concurrent Therapy

The following medications and procedures are prohibited during the study.

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted in this study A DDI with a strong inhibitor would increase MLN2238 exposure. (rationale: if there were to be a drug-drug interaction with an inhibitor, the MLN2238 exposure would be increased leading to a high probability of an adverse event):

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use . A DDI with a strong inducer would decrease MLN2238 exposure Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

The dietary supplements St John's wort and Ginkgo biloba are not permitted.

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against MM except for drugs in this treatment regimen.
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study drug dosing.
- Adjuvant hormone therapy for breast or prostate cancer

3.6 Treatment Compliance

Patients will keep a pill diary.

3.7 Precautions and Restrictions

- Fluid deficits should be corrected before and throughout treatment.

3.8 Contraception Requirements

The effects of MLN9708 on human pregnancy or development of the embryo or fetus are unknown. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet the following eligibility criteria:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- Agree to completely abstain from heterosexual intercourse
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, for at least 30 days before starting study drug through 28 days after the last dose of study treatment.
    - The 2 methods of reliable contraception must include 1 highly effective method and 1 additional effective (barrier) method. Females of childbearing potential must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

      Highly effective methods:

        - Intrauterine device (IUD)
        - Hormonal (birth control pills, injections, implants)

- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

Male patients, even if surgically sterilized (ie, status postvasectomy), must meet the following eligibility criteria:

- Agree to completely abstain from heterosexual intercourse, OR
- Agree to practice effective barrier contraception during the entire study treatment period and through 28 days after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy.

3.9 Duration of Treatment and Patient Participation

. Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Patients will be removed from study for the following reasons.

- Progression of disease
- Patient's request to withdraw from the study or refusal of further therapy
- Unacceptable toxicity
- Pregnancy
- Physicians discretion
- Lost to long term follow up after 12 months of no contact

Definition of Progressive Disease:
Progressive disease (for patients not in CR) requires one or more of the following:

• >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL and confirmed by at least one repeated investigation.
• >25% increase in the 24 hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 hour and confirmed by at least one repeated investigation.
• >25% increase in plasma cells in a bone marrow aspirate or trephine biopsy, which must also be an absolute increase of at least 10%.
• Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

• Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response).
• Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L) not attributable to any other cause.

Relapsed disease (for patients who were in CR) requires at least one or more of the following (to be used for analyzing disease free survival).

• Reappearance of serum or urine monoclonal paraprotein by immunofixation or electrophoresis.
• Development of at least 5% plasma cells in the bone marrow.
• A difference between involved and uninvolved FLC levels of >10 mg/dL, only in patients without measurable paraprotein in the serum and urine.
• Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
• Development of hypercalcemia (corrected serum calcium > 11.5 g/dL or 2.8 mmol/L) not attributable to any other cause.
• Appearance of any other sign of progression.

Patients with relapsed disease (recurrence of disease after attaining a CR) should continue on treatment if they do not fulfill criteria for progressive disease. This would apply to patients at any time following initiation of maintenance therapy.

3.10 Efficacy, Correlative Studies, and Safety Measurements

3.10.1 Efficacy Measurements

Patients will be staged every 1-3 cycles +/- 7 days while on protocol. Efficacy evaluations will be based on changes in myeloma protein measurements in serum and 24-hour urine, bone marrow examination as indicated, skeletal survey as indicated clinically, extramedullary plasmacytomas as clinically indicatedA serum sample for FreeLite ™ testing will be obtained.

3.10.2 Correlative/ QOL Questionnaire

Mandatory blood samples one 50 ml in green top tube and 10 ml in Purple top will be obtained at time of routine blood collection and banked in the MDACC Plasma Cell Dyscrasia Tissue Bank every 1-3 cycles on day 1 +/- 7 days.
The blood samples will be used for future research to better understand myeloma biology, diagnostic and prognostic features and immunoprofiling
M. D. Anderson Symptom Inventory (MDASI-MM module) scores. The core MDASI-MM module is a brief, easily understood instrument that provides a measure of the intensities of 13 cancer-related symptoms. Patients will be asked to rate the intensity of physical, affective, and cognitive symptoms on 0 to 10 numeric scales from “not present"

(score of 0) to "as bad as you can imagine" (score of 10). Patients will also rate the amount of interference with daily activities caused by symptoms on 0 to 10 numeric scales from "did not interfere" (score of 0) to interfered completely (score of 10). Six symptom items determined by physicians and nurses in the Lymphoma/Myeloma and Blood and Marrow Transplantation Departments to be important for the assessment of patients with multiple myeloma and patients who are post-transplant will be added to the core MDASI-MM module for this study. The symptoms to be assessed by the core MDASI-MM module include: pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness, constipation, muscle weakness, diarrhea, mouth or throat sores, rash, and trouble concentrating. The six additional items assessing symptom-related interference in general activity, mood, work, relation with others, enjoyment of life and walking. The MDASI-MM module will be administered in person, by an interactive voice response (IVR) telephone system, or through the use of tablet PCs. The IVR system will asks patients to rate each symptom and interference item on the 0-10 numeric scales using the keypad of a touch-tone telephone.

While on study, patients will complete MDASI on day 1 (+/- 7 days) of every 1-3 cycles of therapy

3.10.3 Safety Measurements

Before starting each cycle, patients will be evaluated for toxicity. Safety evaluations will be based on changes in physical examinations, ECOG Performance Status scores, clinical laboratory findings from pretreatment to the End-of-Treatment Visit, and on the observation or report of any AEs (including laboratory abnormalities reported as AEs) that occur after starting study drug until 30 days after the last dose of study agent and those SAEs (including laboratory abnormalities reported as AEs) occurring after 30 days if considered related to Lenalidomide or MLN 9708. The intensity (severity) of AEs will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.

4. ADVERSE EVENTS

4.1 Adverse Event Definition

An **adverse event** (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

- The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial."
- PDMS/CORe will be used as the electronic case report form (eCRF) and protocol specific data will be entered into PDMS/CORe for patients at MDACC.

We will only capture clinically relevant AE as determined by the treating physician.

For this protocol an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

We will per GCP have an AE log.

4.1.1 Serious Adverse Event Definition/ Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Suspected transmission of infectious agents by a medicinal product

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (**21 CFR 312.32**).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an**

SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, MDACC IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours**

- **Serious adverse events will be captured from the time the patient therapy and until 30 days after therapy discontinues. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to MDACC IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager MDACC IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Reporting to Millennium:

This is an investigator-initiated study. The principal investigator (who may also sometimes be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

Sponsor-investigator must report all SAEs, regardless of expectedness or relationship with any study drug, to Millennium Pharmacovigilance (or designee) as soon as

possible, but no later than 5 calendar days of the sponsor-investigator's observation or awareness of the event. In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Subinvestigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and subinvestigator(s). Millennium Pharmacovigilance (or designee) may request follow-up information to a reported SAE, which the sponsor-investigator will be responsible for providing to Millennium Pharmacovigilance (or designee).

The SAE report must include event term(s), serious criteria, and the investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration.

Intensity for each SAE, including any lab abnormality, will be determined by using the NCI CTCAE, version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study or study drug(s), including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information Fax Number: 1-800-963-6290 Email: TakedaOncoCases@cognizant.com

Suggested Reporting Form:

- **SAE Report Form (a sample is provided in Section 7.10)**
- **US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm**
- **Any other form deemed appropriate by the sponsor-investigator**

4.2 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and must permanently discontinue study drug(s). All pregnancies and suspected pregnancies must be reported to Millennium Pharmacovigilance (or designee; see Section 4.2 for contact information) immediately. The pregnancy must be followed for the final pregnancy outcome (ie, delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance (or designee) immediately (see Section 4.2 for contact information). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

4.3 **Long Term Follow-Up Phase**

Following end of therapy on this trial, all subjects will be followed until death, withdrawal of consent for study participation, or removal from study. Subjects will return to the site or be contacted by telephone every 6 months (+/- 4 weeks) for follow up assessments of the following:

- Second primary malignancies
- Next-line of therapy
- Progressive disease on next line of therapy
- Overall survival

Following disease progression on the next-line of therapy, subjects will only be followed for overall survival and development of 2nd primary malignancies.

5. STATISTICAL CONSIDERATIONS

Design

This is a single-arm, open label, phase II trial to determine the progression free survival (PFS) of patients with multiple myeloma treated with the combination of MLN 9708 with Lenalidomide as maintenance therapy post autologous stem cell transplant.

Analysis plan, Sample Size and Power

The primary endpoint is PFS, defined as the time from autologous stem cell transplantation (ASCT) to the time of clinical progression, death, whichever occurs first or the time of last contact. It is hypothesized that the combination will prolong PFS compared to the current standard regimen. A total of 48 patients (dosed at 3 mg of Ixazomib) will be enrolled at an accrual rate of 2 patients per month over 24 months. Additional 48 months of follow-up is planned after the last patient is recruited into the trial. Assuming that PFS time follows an exponential distribution, and patients treated with the current standard regimens had a median PFS of 40 months, we will monitor the PFS using the method of Thall et al. (Thall, 2005). Let Ts and Te represent the time to progression for the standard regimens and the proposed treatment regimen, respectively. We assume Ts|Ms and Te|Me follow an exponential distribution with respective median Ms and Me. Furthermore, we assume that the prior for Ms follows an inverse gamma distribution IG (100, 3960) to reflect our knowledge of PFS for the patients treated with the standard regimens. This has a mean of 40 months, and a variance of 16.3. The prior for Me is assumed to be IG (3, 80), which has the same mean of 40 months and a larger variance of 1600 to reflect the uncertainty about the median PFS of the proposed treatment regimen.

The PFS will be monitored every six months, and the study will be terminated early if there is little evidence based on the available data that the median PFS of the patients treated with the proposed treatment regimen is 12 months or more than that of the patients treated with the standard regimens. The formal stopping rule is

$$\Pr(Me > Ms+12 \mid data) < 0.035$$

Specifically, the trial will be stopped early if there is less than 3.5% chance that the median PFS for the patients treated with the proposed treatment regimen is 12 months or more than the median PFS for the patients treated with the standard regimens. The probability cutoff 0.035 was chosen to obtain an early stopping probability around 10% (0.091) if the true median PFS for the proposed treatment regimen results in a 12 months improvement over the historical median PFS of 40 months.

The operating characteristics of this decision rule are summarized in Table 1 using the onearmTTE software developed at the Department of Biostatistics at M.D. Anderson.

Table 1. Operating characteristics for the design (based on 2000 simulations)

True median Progression Free Survival (month)	Pr(stop early)	Average Number of Patients Treated (25th, 75th percentiles)
30	0.92	39.6 (32, 48)

36	0.64	42.9 (42, 48)
40	0.41	44.4 (48, 48)
48	0.16	46.0 (48, 48)
52	0.091	46.5 (48, 48)
60	0.053	46.9 (48, 48)

This monitoring will be carried out via the Clinical Trial Conduct (CTC) website (https://biostatistics.mdanderson.org/ClinicalTrialConduct) which is housed on a secure server at MDACC and maintained by the MDACC Department of Biostatistics. Access to the website will be gained through usernames and passwords provided by the MDACC Department of Biostatistics. Training on the use of the CTC will be provided by the biostatistical collaborator of the study, with emphasis on the importance of timely updating of follow-up times and recording of events. The monitoring rules for the PFS will be applied every six months with the probability criterion recomputed based on the most recent data available at that time. If the stopping rule is met, the study statistician, research nurse, and principal investigator will each receive an email notification that the stopping boundary has been met.

Because of the limited number of patients who have received the combination treatment, we will monitor the toxicity of the combination while we monitor the efficacy of it. Due to the lack of detailed information about the association between toxicity and efficacy, independency between the efficacy endpoints and toxicity endpoints is assumed, and the toxicity events are monitored continuously (Thall et al., 1996). The toxicity endpoint is defined as treatment-related unmanageable toxicities, including grade 3 non-hematologic effects, or grade 4 hematologic effects, that require delay or termination of the treatment during cycle 1 A toxicity rate of 30% or higher will not be considered acceptable. The prior probability of toxicity is assumed to follow a Beta (0.3, 0.7) distribution with one patient worth of information. The toxicity will be monitored by a cohort size of 4. At any time after at least 4 patients have completed toxicity evaluations, the trial will be stopped if the following statement is true

$$\Pr[\text{toxicity rate} > 30\% \mid \text{data}] > 0.95,$$

which means that the trial will be stopped for toxicity if the posterior probability of the toxicity rate being greater than 30% is greater 95%. The early stopping boundaries for toxicity, shown in the format of

(The number of patients with toxicities) / (The number of patients treated),
are ≥3/4, 5/8, 7/12, 9/16, 10/20, 12/24, 13/28, 15/32, 16/36, 18/40, 19/44, and 21/48.

Table 2. Operating characteristics for the stopping rules
For excessive toxicity monitoring

True DLT Rate	Probability Stop Early	Mean sample size
0.20	0.035	46.5
0.30	0.18	41.8
0.40	0.56	30.7
0.45	0.77	23.8
0.50	0.91	17.8

Early termination of the trial can be caused by either lack of efficacy or excessive toxicity. If the efficacy and toxicity are considered jointly, the early stopping probabilities as shown in Table 3 will be higher than the probabilities shown in Tables 1 to 2.

Table 3: Operating characteristics considering efficacy and toxicity jointly

True median	True toxicity rate	Probability Stop Early
36	0.2	0.65
36	0.3	0.70
36	0.5	0.97
52	0.2	0.12
52	0.3	0.25
52	0.5	0.92
60	0.2	0.086
60	0.3	0.22
60	0.5	0.91

Patients' demographic and clinical characteristics at baseline will be summarized using descriptive statistics such as frequency distribution, mean (± s.d.) and median (range) accompanied by graphical analysis. Student t-test/Wilcoxon test and ANOVA/Kruskal-Wallis test will be used to compare continuous variables between different patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables (Woolson, 2002).

The response rates and incidence of new primary malignancy will be estimated along with 95% confidence intervals. Time-to-event outcomes, including PFS and overall survival (OS), will be estimated using the Kaplan-Meier method (Kaplan, 1958). log-rank test will be performed to test the difference in time-to-event distributions between patient groups (Mantel, 1966). Cox proportional hazards model will be used to include multiple covariates in the time-to-event analysis (Cox, 1972).

Toxicity data will be summarized by frequency tables. For the toxicity endpoint, per-treated analysis will be used to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received.

The MDASI –myeloma symptom evaluation will be analyzed with descriptive analysis.

6. PRODUCT COMPLAINTS

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

For Product Complaints,
Phone: 1-877-TAKEDA7 (1-877-825-3327)
- E-mail: medicalinformation@tpna.com
- FAX: 1-800-247-8860
- Hours: Mon-Fri, 8 a.m. – 6 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance.

7.ADMINISTRATIVE REQUIREMENTS

7.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and IB. Essential clinical

documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. This is the responsibility of the sponsor-investigator.

7.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Millennium requests that the protocol and informed consent documents be reviewed by Millennium prior to IRB/IEC submission.

7.3 Patient Information and Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risk Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

7.4 Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

7.5 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports, and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority(ies) access to the patient's

original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

7.6 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

7.7 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

7.8 Drug Accountability

Accountability for the drug at all study sites (including all subsites, if applicable) is the responsibility of the sponsor-investigator. The sponsor-investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Millennium or disposal of the drug will be maintained by the site and/or subsites. Accountability records will include drug receipt/destruction dates, quantities, lot numbers, expiration dates (if applicable), and corresponding registered patient numbers.

All material containing MLN9708 will be treated and disposed of as hazardous waste in accordance with governing regulations.

7.9 Record Retention

The sponsor-investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

8. APPENDICES

8.1 Study Flow Chart

Procedure	Screening ≤ 28 days from Initiation of therapy (may include Day 1)	Baseline	Cycle 1: (except cycle 1 day 1[8])8			all cycles beyond cycle 1	End of study	Follow up
		Cycle 1 Day 1 +/- 7 days	Day 8 +/-3 days (only dose escalation phase)	Day 15 +/-3 days (only dose escalation phase)		Day 1 +/-7 days	within 30 days after last dose +/- 7 days	Every 6 months (+/- 4 weeks)
Informed consent	X							
Inclusion/Exclusion criteria	X							
Complete Medical Hx	X							
Confirmation Dx and status of disease and prior Rx	X							
MDASSI Questionnaire and Correlative Samples[6]		X				X[6]		
Record concurrent therapies/procedures	X							
Record adverse events	X	X				X	X	
Physical examination, vital signs Score7	X	X	X	X		X	X	
Skeletal survey(as clinically indicated)	X						X	
Bone Marrow aspiration and biopsy	X					X[1]	X	
12 Lead ECG	X							
Hematology[3]	X[4]	X	X	X		X	X	
Serum chemistry[2]	X[4]	X	X	X		X	X[4]	
TSH	x							
Ht, Wt, BSA	X	X				X	X	
Pregnancy test for females of child bearing potential	X	X[5]				X[5]	X	
Register Patient into Rev Assist® Program	X							
Serum and urine M component quantification	X					X (every 1-3 cycles	X	
24hour urine for protein measurement	X					X (every 1-3 cycles	X	
Prescribe lenalidomide via RevAssist®		X				X		
Serum for FreeLite Testing	X					X (every 1-3 cycles	X	
Dispense study drug for next cycle		X				X		
Perform drug accountability			X			X	X	
Survival status								X[8]

1. A repeat bone marrow biopsy will only be done at time of suspected complete remission to document complete remission per standard clinical practice and at physician discretion.
2. To include Na, K, Cl, Co2, Ca, Mg, Phosphorous, BUN, Cr., glucose, albumin, alk phos, total Bili, ast/alt.
3. WBC, differential, Hgb, Hct and platelet count
4. Screening CBC and Chemistry parameters need to meet criteria to initiate dosing in section 3.1 within 5 days of starting protocol directed therapy.
5. Pregnancy testing will be done 10-14 days prior to starting therapy and within 24 hours prior of starting lenalidomide on day 1
6. These will be done ever 1-3 cycles.

7. DAY 8 AND DAY 15 (+/-) 3 DAYS ASSESSMENTS ARE TO BE DONE DURING CYCLE 1 AND DURING THE CYCLE THE PHYSICIAN DOSE ESCALATES

8. Subjects will return to the site or be contacted by telephone every 6 months (+/- 4 weeks) for follow up assessments, refer to section 4.3.

8.2 Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5	Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5(6):649-55.

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