Supplemental Data

Oral ixazomib, lenalidomide, and dexamethasone for newly diagnosed transplant-ineligible multiple myeloma patients

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TOURMALINE-MM2 Collaborators

Patients were recruited from 157 centers across eight countries in Europe, North America, and the Asia-Pacific region. These countries were as follows:
Belgium, Canada, France, Japan, Republic of Korea, New Zealand, Russia, United States of America

Supplemental methods

Patients

Adult patients with a confirmed diagnosis of symptomatic multiple myeloma according to International Myeloma Working Group (IMWG) criteria and who were eligible for treatment with lenalidomide-dexamethasone but ineligible for autologous stem cell transplant due to age (≥65 years) or comorbidities were enrolled. Eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0-2 and adequate hematologic and hepatic function. Patients with mild-to-moderate renal function impairment (calculated creatinine clearance ≥30 mL/min) were included. Patients with peripheral neuropathy of grade ≥2 or grade 1 with pain and patients with uncontrolled cardiovascular conditions were not eligible (see Supplemental Table 1 for detailed eligibility criteria).

Brief Pain Inventory-Short Form questionnaire

The Brief Pain Inventory-Short Form (BPI-SF) contains 15 items designed to capture the pain severity ("worst," "least," "average," and "now" [current pain]), pain location, medication to relieve the pain, and the interference of pain with various daily activities including general activity, mood, walking activity, normal work, relations with other people, sleep, and enjoyment of life. The questionnaire employs a 24-hour recall period. The pain severity items are rated on a 0 to 10 scale, with 0 = no pain and 10 = worst pain.

At the time of each pain assessment including unscheduled visits, the patient was queried regarding concomitant use of analgesics, if any. The patient-recalled amount of analgesic use during the 24 hours prior to pain assessment was recorded on both the 24-hour analgesic form and concomitant medication electronic case report forms. Patients completed the BPI-SF at screening, and on Day 1 of each cycle until disease progression, to capture the effect of pain on patients' daily activities and patient-reported analgesic use, and to collect the pain severity, location, and interference information with a 24-hour recall period. This was completed prior to other assessments or study drug regimen being administered. A pain response was defined as the occurrence of at least a 30% reduction from baseline in BPI-SF worst

pain score over the previous 24 hours without an increase in analgesic use for two consecutive measurements at least 28 days apart.

The use of the single item, worst pain, is supported by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for assessing pain in clinical trials and by the European Medicines Agency 2003 Guidance on Clinical Investigation of Medicinal Products for Nociceptive Pain issued by the Committee for Proprietary Medicinal Products.

Prophylactic medications and permitted concomitant treatments

- Thromboprophylaxis with aspirin or low-molecular-weight heparin was required while patients were receiving lenalidomide.
- Myeloid growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) were permitted. Their use should follow the product label, published guidelines and/or institutional practice.
- Erythropoietin was allowed in this study, but given the potential increased risk of deep vein thrombosis when erythropoietin is administered concurrent with lenalidomide, the use of erythropoietin was minimized as much as possible.
- Patients were transfused with red cells and platelets as clinically indicated.
- Concomitant treatment with bisphosphonates was encouraged for all patients with evidence of lytic destruction of bone or with osteopenia, according to the American Society of Clinical Oncology Clinical Practice Guidelines or institutional practice in accordance with the product label, unless specifically contraindicated. If bisphosphonate therapy was not started prior to the study start, it was initiated as soon as clinically indicated.
- Supportive measures consistent with optimal patient care could be given throughout the study.
- Dose adjustments for toxicities were permitted using established dose-modification guidelines per the protocol/prescribing information for each drug.

Assessment of cytogenetic abnormalities and minimal residual disease

Cytogenetic abnormalities were assessed by a central laboratory using a bone marrow aspirate sample taken at screening The sample obtained at screening (within 8 weeks of randomization) was used for molecular analyses and for evaluation of cytogenetics covering a panel of high-risk abnormalities including the following: t(4;14), t(14;16), del(17p) and amp(1q21). Per protocol, the cutoff values for defining the presence of expanded high-risk cytogenetic abnormalities were established by the central diagnostic laboratory on the basis of the false positive rates (or technical cutoff values) of the FISH probes that were used. These cutoff points were 5% positive cells for del(17p), 3% positive cells for t(4;14) and t(14;16), and 20% positive cells for amp(1q21). This aspirate sample was also used to assess mutation status of genes in key pathways, such as Ras/Raf, and to assess activity of key signaling pathways determined to be clinically meaningful, such as non-canonical nuclear factor-kappa-B pathway activation and protein synthesis.

Minimal residual disease (MRD) was assessed by flow cytometry at a sensitivity of 10^{-5}. A bone marrow aspirate was collected for assessment of MRD in all patients suspected to have reached complete response (CR) anytime during the entire conduct of the study. In addition, a second bone marrow aspirate for MRD assessment was collected at cycle 18 in patients who maintained a CR until that point (this sample could be collected up to 4 weeks after cycle 18). If a patient had MRD testing because of a suspected CR within 2 cycles of cycle 18, then this repeat MRD assessment was not performed.

Patient-reported quality of life and healthcare resource utilization assessments

Health-related quality of life (HRQoL) was evaluated through patient self-reported instruments including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30 and MY-20). The EORTC QLQ-30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), one global health status scale, three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The time recall period for this instrument is 1 week (the week immediately preceding the assessment).

The MY-20 multiple myeloma module (20-items) has four independent subscales, two functional subscales (body image, future perspective), and two symptoms scales (disease symptoms and side-effects of treatment). This was administered subsequent to the EORTC QLQ-C30.

These QoL assessments were obtained at screening, and on Day 1 of each cycle until disease progression or treatment discontinuation for all possible reasons, and was completed before other assessments were performed or any drug in the study drug regimen was administered. These are reliable and valid measures of HRQoL in patients with cancer and take about 15 minutes to administer. The instruments consist of a total of 50 items and have been validated and used in many countries.

Healthcare resource utilization data were summarized by descriptive statistics of medical encounters (number and rates of encounters, reasons for encounters, and length of stay) for hospitalizations, emergency department visits, and outpatient visits.

Definition of analysis populations

Intent-to-treat population: All patients who were randomized. Patients were analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

Safety population: All patients who received at least 1 dose of any study drug. Patients were analyzed according to the treatment actually received. That is, those patients who were randomized to the active arm but received the regimen in the control arm were included in the control arm; those patients who were randomized to the control arm but received the regimen in the active arm were included in the active arm for safety analyses.

Per-protocol population: All patients who did not have major protocol violations, as determined by the study clinician, who was blinded to study drug assignment.

Supplemental Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adult male or female patients 18 years old and above with a confirmed diagnosis of symptomatic multiple myeloma according to IMWG criteria who have not received prior treatment for multiple myeloma • Patients for whom lenalidomide and dexamethasone treatment is appropriate and who are not eligible for HDT-SCT for one or more of the following reasons: o The patient is 65 years of age or older o The patient is less than 65 years of age but has significant comorbid condition(s) that are, in the opinion of the investigator, likely to have a negative impact on tolerability of HDT-SCT • Patients must have measurable disease defined by at least one of the following three measurements: o Serum M-protein ≥1 g/dL (≥10 g/L) o Urine M-protein ≥200 mg/24 hours o Serum free light chain assay: involved free light chain level ≥10 mg/dL (≥100 mg/L), provided that the serum free light chain ratio is abnormal	• Prior treatment for multiple myeloma with either standard of care treatment or investigational regimen. NOTE: Prior treatment with corticosteroids or localized radiotherapy is permitted as long as it is below a therapeutic level (maximum dose of corticosteroids should not exceed the equivalent of 160 mg of dexamethasone over a 2-week period) • Localized radiotherapy within 14 days before randomization • Diagnosed and treated for another malignancy within 5 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone histologically confirmed complete surgical resection • Inability or unwillingness to receive thromboembolism prophylaxis

• Patients must meet the following clinical laboratory criteria: o ANC ≥1000/mm^3 and platelet count ≥75000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to randomization o Total bilirubin ≤1.5 × ULN. o ALT and AST ≤3 × ULN. o Calculated creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault Equation. NOTE: Patients with a low creatinine clearance ≤60 mL/min (or ≤50 mL/min, according to local label/practice) but ≥30 mL/min will receive a reduced lenalidomide dose of 10 mg QD on Days 1 through 21 of a 28-day cycle; patients with a creatinine clearance <30 mL/min are not permitted to be enrolled into the study. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (i.e., creatinine clearance >60 mL/min or >50 mL/min, according to local	• Female patients who are lactating and breastfeeding or have a positive pregnancy test during the screening period • Major surgery within 14 days before randomization. NOTE: Kyphoplasty or vertebroplasty is not considered major surgery • Central nervous system involvement • Infection requiring systemic antibiotic therapy or other serious infection within 14 days before randomization • Diagnosis of Waldenstrom's macroglobulinemia, POEMS syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome • Evidence of current uncontrolled cardiovascular conditions within 6 months prior to randomization, including: o Uncontrolled hypertension, cardiac arrhythmias, or congestive heart failure o Unstable angina, or o Myocardial infarction • Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole,

label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg QD • ECOG performance status of 0, 1, or 2. • Female patients who: o Are postmenopausal for at least 24 months before the Screening visit, OR o Are surgically sterile, OR o FCBP must: ▪ a. All countries except Canada: Have TWO medically-supervised negative pregnancy tests (serum or urine with sensitivity of at least 25 mIU/mL), even if continuous abstinence is the chosen method of contraception. One test must be obtained within 10 to 14 days and the other test must be obtained within 24 hours prior to administering the first dose of the study drug regimen at cycle 1, day 1. The dates and results of pregnancy tests must be documented ▪ b. Canada: Have TWO medically supervised negative serum pregnancy tests with a sensitivity	voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before randomization in the study • Ongoing or active infection, or active hepatitis B or C infection, or known human immunodeficiency virus positive • Comorbid systemic illnesses or other severe concurrent disease which, 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 (e.g., peripheral neuropathy that is grade 1 with pain or grade 2 or higher of any cause) • Psychiatric illness/social situation that would limit compliance with study requirements • Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent

of at least 25 mIU/mL prior to the first dose of the study drug regimen, even if continuous abstinence is the chosen method of contraception. One test must be obtained within 7 to 14 days and the second within 24 hours prior to administering the first dose of the study drug regimen at cycle 1, day 1. The dates and results of pregnancy tests must be documented ▪ c. Either agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception) OR begin TWO reliable methods of birth control: 1 highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting the study drug regimen through 90 days after the last dose of study treatment ▪ d. Agree to ongoing pregnancy testing	• 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 • Treatment with any investigational products within 60 days before randomization

▪ e. Adhere to the guidelines of the Revlimid REMS™ (formerly known as RevAssist®) program (US participants), RevAid® program (Canadian participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial Revlimid supplies). The counseling must be documented. Male patients, even if surgically sterilized (i.e., status postvasectomy), must: o Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception) OR o Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy, AND	

o Adhere to the guidelines of the Revlimid REMS™ (formerly known as RevAssist®) program (US participants), RevAid® program (Canadian participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial Revlimid supplies). The counseling must be documented • Suitable venous access for the study-required blood sampling • Must be able to take concurrent aspirin 70 to 325 mg daily (or equivalent dose per country product label (PI or SmPC) or enoxaparin 40 mg subcutaneously daily (or its equivalent) if allergic to aspirin, per published standard or institutional standard of care, as prophylactic anticoagulation prior to randomization. NOTE: For patients with prior history of DVT, LMWH is mandatory. • Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that	

consent may be withdrawn by the patient at any time without prejudice to future medical care • Patient is willing and able to adhere to the study visit schedule and other protocol requirements	

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CYP3A, cytochrome P4503A; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; FCBP, females of childbearing potential; GI, gastrointestinal; HDT-SCT, High-dose therapy and stem cell transplantation; IMWG, International Myeloma Working Group; LMWH, low molecular weight heparin; PI, package insert; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; QD, *quaque die* (once a day); SmPC, Summary of Product Characteristics; ULN, upper limit of the normal range; US, United States.

Supplemental Table 2. PFS events and reasons for censoring patients* in the intent-to-treat population.

	Ixazomib-Rd N = 351	Placebo-Rd N = 354
PFS events, n (%)	**169 (48.1)**	**209 (59.0)**
Progression	132 (37.6)	182 (51.4)
Death	37 (10.5)	27 (7.6)
Patients censored, n (%)	**182 (51.9)**	**145 (41.0)**
No documented death or PD	85 (24.2)	80 (22.6)
Alternate therapy	60 (17.1)	47 (13.3)
Withdrawal of consent	20 (5.7)	4 (1.1)
Death or PD after >1 missed visit	12 (3.4)	10 (2.8)
No baseline or no post-baseline assessment	3 (0.9)	1 (0.3)
Lost to follow-up	2 (0.6)	3 (0.8)

FDA, Food and Drug Administration; PD, progressive disease; PFS, progression-free survival.

*Censoring was per FDA censoring rules.

Supplemental Table 3. Patient demographics, and cause of early death, among 27 patients who died in the absence of disease progression within 6 months of randomization

	Ixazomib-Rd N = 351	Placebo-Rd N = 354
Patients who died in the absence of PD within 6 months of randomization, n (%)*	**18**	**9**
Patient demographics, n (%)	**n = 18**	**n = 9**
Age categories		
<75 years	10 (55.6)	4 (44.4)
≥75 years	8 (44.4)	5 (55.6)
ECOG PS		
0-1	13 (72.2)	7 (77.8)
2	5 (27.8)	2 (22.2)
Cause of death, n		
Sepsis	3	4
Cardiac arrest	2	0
Plasma cell myeloma	2	0
Pneumonia	2	0
Cerebral hematoma	1	0
General health deterioration	1	1
Intestinal perforation	1	0
Ischemic cardiomyopathy	1	0
MM progression and pneumonia	1	0
Respiratory distress	1	0
Respiratory failure	1	0

No cause given	1	1
Sudden death	1	1
Failure to thrive	0	1
Myocardial infarction	0	1

ECOG PS, Eastern Cooperative Oncology Group Performance Status; MM, multiple myeloma; PD, progressive disease.
*For patients receiving ixazomib-Rd and placebo-Rd, respectively, n=5 and n=2 deaths were deemed related to study treatment, n=7 and n=4 deaths were deemed related to disease under study, and n=6 and n=3 deaths were deemed unrelated to study treatment or disease under study.

Supplemental Table 4. Summary of new-onset TEAEs during the first and second phases of treatment

Treatment group	Ixazomib-Rd,* N = 354			Placebo-Rd,* N = 349		
Subgroup by number of cycles of treatment received	<19, n = 163	≥19, n = 191		<19, n = 160	≥19, n = 189	
Overall rates of TEAEs, n (%)						
Period of new-onset events, cycles	1-18	1-18	≥19	1-18	1-18	≥19
Any TEAE	163 (100)	191 (100)	184 (96.3)	160 (100)	189 (100)	170 (89.9)
Any drug-related TEAE	155 (95.1)	183 (95.8)	145 (75.9)	142 (88.8)	175 (92.6)	112 (59.3)
Any grade ≥3 TEAE	147 (90.2)	133 (69.6)	115 (60.2)	131 (81.9)	121 (64.0)	90 (47.6)
Any drug-related grade ≥3 TEAE	117 (71.8)	104 (54.5)	71 (37.2)	92 (57.5)	85 (45.0)	50 (26.5)
Any serious TEAE	119 (73.0)	66 (34.6)	83 (43.5)	105 (65.6)	77 (40.7)	63 (33.3)
Any drug-related serious TEAE	74 (45.4)	37 (19.4)	38 (19.9)	53 (33.1)	35 (18.5)	24 (12.7)
TEAE resulting in dose reduction of ≥1 of the three agents in the regimen	73 (44.8)	121 (63.4)	44 (23.0)	78 (48.8)	96 (50.8)	23 (12.2)
TEAE resulting in discontinuation of ≥1 of the three agents in the regimen	103 (63.2)	22 (11.5)	37 (19.4)	72 (45.0)	10 (5.3)	27 (14.3)
TEAE resulting in dose discontinuation of the full study drug regimen	99 (60.7)	0	25 (13.1)	66 (41.3)	0	28 (14.8)
On-study deaths	21 (12.9)	0	6 (3.1)	17 (10.6)	0	5 (2.6)

Rd, lenalidomide-dexamethasone; TEAEs, treatment-emergent adverse events.

*Dexamethasone discontinued after cycle 18.

Supplemental Table 5. New-onset TEAEs during the second phase of treatment (cycle 19 onwards) among patients receiving ≥19 cycles of treatment

	Ixazomib-Rd,* N = 191		Placebo-Rd,* N = 189	
MedDRA preferred term, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	88 (46.1)	8 (4.2)	64 (33.9)	2 (1.1)
Rash†	39 (20.4)	2 (1.0)	16 (8.5)	1 (0.5)
Peripheral edema	33 (17.3)	0	21 (11.1)	0
Constipation	20 (10.5)	1 (0.5)	20 (10.6)	0
Nausea	27 (14.1)	0	20 (10.6)	0
Peripheral neuropathy†	48 (25.1)	3 (1.6)	23 (12.2)	0
Fatigue	21 (11.0)	1 (0.5)	20 (10.6)	2 (1.1)
Anemia	24 (12.6)	9 (4.7)	16 (8.5)	9 (4.8)
Vomiting	24 (12.6)	1 (0.5)	12 (6.3)	0
Cardiac arrhythmias†	24 (12.6)	11 (5.8)	21 (11.1)	4 (2.1)
Thrombocytopenia†	21 (11.0)	9 (4.7)	4 (2.1)	2 (1.1)
Neutropenia†	37 (19.4)	31 (16.2)	33 (17.5)	31 (16.4)
Pneumonia	21 (11.0)	9 (4.7)	12 (6.3)	4 (2.1)
Acute renal failure†	12 (6.3)	5 (2.6)	14 (7.4)	3 (1.6)
Hypotension†	8 (4.2)	1 (0.5)	6 (3.2)	1 (0.5)
Heart failure†	7 (3.7)	4 (2.1)	4 (2.1)	2 (1.1)
Liver impairment†	8 (4.2)	1 (0.5)	7 (3.7)	2 (1.1)
Myocardial infarction†	2 (1.0)	1 (0.5)	2 (1.1)	2 (1.1)
Encephalopathy†	5 (2.6)	2 (1.0)	1 (0.5)	0

AECI, adverse events of clinical importance; MedDRA, Medical Dictionary for Regulatory Activities; Rd, lenalidomide-dexamethasone; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

*Dexamethasone discontinued after cycle 18.

†Higher-level term, SMQ, or pooled term incorporating multiple preferred terms. “Rash” included the preferred terms of rash maculopapular, rash macular, pruritus, rash, rash erythematous, rash papular, pruritus generalized, urticaria, drug eruption, rash pruritic, dermatitis acneiform, purpura, dermatitis allergic, rash generalized, erythema multiforme, rash vesicular, rash morbilliform, Stevens-Johnson syndrome, exfoliative rash, rash follicular, toxic epidermal necrolysis, rash pustular. “Peripheral neuropathy” included the preferred terms of peripheral sensory neuropathy, neuropathy peripheral, peripheral sensorimotor neuropathy, peripheral motor neuropathy. “Cardiac arrhythmias” included the preferred terms of syncope, atrial fibrillation, palpitations, sinus tachycardia, bradycardia, tachycardia, atrioventricular block complete, cardiac arrest, atrial flutter, supraventricular tachycardia, loss of consciousness, sudden death, sinus bradycardia, ventricular extrasystoles, atrioventricular block, arrhythmia, heart rate irregular, bundle branch block right, supraventricular extrasystoles, atrioventricular block first degree, extrasystoles, heart rate increased, sinus node dysfunction, bundle

branch block left, electrocardiogram QT prolonged, ventricular tachycardia, cardio-respiratory arrest, heart rate decreased. “Thrombocytopenia” included the preferred terms of thrombocytopenia, platelet count decreased. “Neutropenia” included the preferred terms of neutropenia, neutrophil count decreased. “Acute renal failure” included the preferred terms of blood creatinine increased, acute kidney injury, renal failure, renal impairment, creatinine renal clearance decreased, oliguria, azotemia, nephritis, glomerular filtration rate decreased, proteinuria, renal tubular disorder. “Hypotension” included the preferred terms of hypotension, orthostatic hypotension, anaphylactic reaction. “Heart failure” included the preferred terms of cardiac failure, pulmonary edema, cardiac failure congestive, cardiomegaly, diastolic dysfunction, orthopnea, acute pulmonary edema, pulmonary congestion, right ventricular failure, left ventricular failure. “Liver impairment” included the preferred terms of alanine aminotransferase increased, hypoalbuminemia, aspartate aminotransferase increased, hepatocellular injury, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hyperbilirubinemia, hepatic steatosis, liver function test increased, drug-induced liver injury, hepatic cirrhosis, hepatic function abnormal, cholestasis, hepatic encephalopathy, hepatic enzyme increased, blood bilirubin increased, ascites, hepatitis cholestatic, liver disorder. “Myocardial infarction” included the preferred terms of acute coronary syndrome, angina unstable, acute myocardial infarction, blood creatine phosphokinase increased, coronary artery occlusion, electrocardiogram ST segment elevation, myocardial infarction, troponin increased. “Encephalopathy” included the preferred terms of delirium, hepatic encephalopathy, leukoencephalopathy, encephalopathy, hypoxic-ischemic encephalopathy, posterior reversible encephalopathy syndrome.

Supplemental Table 6. Timing of first-onset TEAEs and of TEAEs resulting in discontinuation of ≥1 of the agents in the treatment regimen

	Ixazomib-Rd, N = 354		Placebo-Rd, N = 349	
TEAE*	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any GI event (nausea, vomiting, diarrhea)†, n	265	41	204	9
Within 0-3 months, n (%)	158 (44.6)	16 (4.5)	111 (31.8)	1 (0.3)
After 3-6 months, n (%)	31 (8.8)	4 (1.1)	20 (5.7)	1 (0.3)
After >6 months, n (%)	80 (22.6)	21 (5.9)	76 (21.8)	7 (2.0)
Nausea, n	131	5	97	1
Within 0-3 months, n (%)	81 (22.9)	3 (0.8)	60 (17.2)	1 (0.3)
After 3-6 months, n (%)	12 (3.4)	2 (0.6)	11 (3.2)	0
After >6 months, n (%)	38 (10.7)	0	26 (7.4)	0
Vomiting, n	105	4	46	2
Within 0-3 months, n (%)	69 (19.5)	3 (0.8)	25 (7.2)	1 (0.3)
After 3-6 months, n (%)	11 (3.1)	0	4 (1.1)	1 (0.3)
After >6 months, n (%)	25 (7.1)	1 (0.3)	17 (4.9)	0
Diarrhea, n	216	35	161	7
Within 0-3 months, n (%)	92 (26.0)	12 (3.4)	59 (16.9)	0
After 3-6 months, n (%)	28 (7.9)	2 (0.6)	19 (5.4)	0
After >6 months, n (%)	96 (27.1)	21 (5.9)	83 (23.8)	7 (2.0)
Constipation, n	151	4	144	3
Within 0-3 months, n (%)	119 (33.6)	2 (0.6)	110 (31.5)	2 (0.6)
After 3-6 months, n (%)	8 (2.3)	0	17 (4.9)	0
After >6 months, n (%)	24 (6.8)	2 (0.6)	17 (4.9)	1 (0.3)
Rash‡, n	199	59	130	26
Within 0-3 months, n (%)	158 (44.6)	49 (13.8)	97 (27.8)	17 (4.9)
After 3-6 months, n (%)	13 (3.7)	5 (1.4)	11 (3.2)	4 (1.1)
After >6 months, n (%)	28 (7.9)	5 (1.4)	22 (6.3)	5 (1.4)
Peripheral neuropathy‡, n	120	8	96	4
Within 0-3 months, n (%)	39 (11.0)	2 (0.6)	34 (9.7)	2 (0.6)
After 3-6 months, n (%)	24 (6.8)	2 (0.6)	13 (3.7)	0
After >6 months, n (%)	57 (16.1)	4 (1.1)	49 (14.0)	2 (0.6)
Thrombocytopenia‡, n	73	47	33	16
Within 0-3 months, n (%)	41 (11.6)	22 (6.2)	13 (3.7)	6 (1.7)
After 3-6 months, n (%)	7 (2.0)	7 (2.0)	5 (1.4)	2 (0.6)
After >6 months, n (%)	25 (7.1)	18 (5.1)	15 (4.3)	8 (2.3)
Neutropenia‡, n	71	60	104	94
Within 0-3 months, n (%)	28 (7.9)	24 (6.8)	55 (15.8)	43 (12.3)
After 3-6 months, n (%)	6 (1.7)	3 (0.8)	13 (3.7)	13 (3.7)
After >6 months, n (%)	37 (10.5)	33 (9.3)	36 (10.3)	38 (10.9)
Combined cardiac events†, n	105	47	85	37
Within 0-3 months, n (%)	48 (13.6)	19 (5.4)	29 (8.3)	14 (4.0)

After 3-6 months, n (%)	14 (4.0)	7 (2.0)	18 (5.2)	8 (2.3)
After >6 months, n (%)	46 (13.0)	21 (5.9)	42 (12.0)	15 (4.3)
Cardiac arrhythmias‡, n	81	30	74	25
Within 0-3 months, n (%)	32 (9.0)	11 (3.1)	23 (6.6)	10 (2.9)
After 3-6 months, n (%)	12 (3.4)	5 (1.4)	15 (4.3)	6 (1.7)
After >6 months, n (%)	37 (10.5)	14 (4.0)	36 (10.3)	9 (2.6)
Heart failure‡, n	32	15	21	9
Within 0-3 months, n (%)	16 (4.5)	6 (1.7)	5 (1.4)	1 (0.3)
After 3-6 months, n (%)	4 (1.1)	2 (0.6)	4 (1.1)	2 (0.6)
After >6 months, n (%)	12 (3.4)	7 (2.0)	12 (3.4)	6 (1.7)
Myocardial infarction‡, n	11	5	9	7
Within 0-3 months, n (%)	4 (1.1)	3 (0.8)	3 (0.9)	3 (0.9)
After 3-6 months, n (%)	3 (0.8)	0	2 (0.6)	0
After >6 months, n (%)	4 (1.1)	2 (0.6)	4 (1.1)	4 (1.1)
Acute renal failure‡, n	58	23	65	26
Within 0-3 months, n (%)	25 (7.1)	10 (2.8)	27 (7.7)	13 (3.7)
After 3-6 months, n (%)	14 (4.0)	4 (1.1)	10 (2.9)	5 (1.4)
After >6 months, n (%)	19 (5.4)	9 (2.5)	28 (8.0)	8 (2.3)
Hypotension‡, n	41	8	29	7
Within 0-3 months, n (%)	21 (5.9)	4 (1.1)	18 (5.2)	3 (0.9)
After 3-6 months, n (%)	7 (2.0)	0	2 (0.6)	2 (0.6)
After >6 months, n (%)	13 (3.7)	4 (1.1)	9 (2.6)	2 (0.6)
Liver impairment‡, n	31	9	27	9
Within 0-3 months, n (%)	15 (4.2)	6 (1.7)	8 (2.3)	4 (1.1)
After 3-6 months, n (%)	2 (0.6)	1 (0.3)	6 (1.7)	1 (0.3)
After >6 months, n (%)	14 (4.0)	2 (0.6)	13 (3.7)	4 (1.1)
Encephalopathy‡, n	8	3	7	4
Within 0-3 months, n (%)	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
After 3-6 months, n (%)	1 (0.3)	0	0	0
After >6 months, n (%)	5 (1.4)	2 (0.6)	5 (1.4)	3 (0.9)
TEAEs resulting in discontinuation of ≥1 agent, n	162		109	
Within 0-3 months (0-90 days)§, n (%)	66 (18.6)		33 (9.5)	
After 3-6 months (91-180 days) §, n (%)	19 (5.4)		13 (3.7)	
After >6 months (>180 days) §, n (%)	77 (21.8)		63 (18.1)	

GI, gastrointestinal; Rd, lenalidomide-dexamethasone; TEAE, treatment-emergent adverse event.

*For analysis of each AECI, patients were counted only once. Patients could have had multiple events and the earliest one was used to calculate the total.

†For analysis of combined GIs and combined cardiac AECIs, patients could be counted within more than one time period if experiencing first onset of individual AECIs within different time periods.

‡See Supplemental Table 5 footnotes.

§From first dose.

Supplemental Table 7. Most common treatment-emergent adverse events resulting in dose reductions and discontinuations

MedDRA preferred term, n (%)	Ixazomib-Rd, N = 354	Placebo-Rd, N = 349
TEAE resulting in dose reduction of ≥1 of the three agents in the study drug regimen (≥3% in either arm)		
Any	211 (59.6)	189 (54.2)
Maculopapular rash	31 (8.8)	17 (4.9)
Peripheral sensory neuropathy	30 (8.5)	6 (1.7)
Diarrhea	22 (6.2)	10 (2.9)
Neutropenia	18 (5.1)	33 (9.5)
Peripheral edema	18 (5.1)	14 (4.0)
Insomnia	12 (3.4)	14 (4.0)
Thrombocytopenia	12 (3.4)	4 (1.1)
Fatigue	11 (3.1)	8 (2.3)
TEAE resulting in discontinuation of ≥1 of the three agents in the study drug regimen (≥2% in either arm)		
Any	160 (45.2)	108 (30.9)
Maculopapular rash	11 (3.1)	1 (0.3)
Peripheral sensory neuropathy	11 (3.1)	6 (1.7)
Diarrhea	9 (2.5)	1 (0.3)
Pneumonia	7 (2.0)	0
TEAE resulting in all study drugs discontinuation (≥1.5% in either arm)		
Any	122 (34.5)	93 (26.6)
Diarrhea	9 (2.5)	1 (0.3)
Pneumonia	6 (1.7)	0
Peripheral sensory neuropathy	4 (1.1)	6 (1.7)

MedDRA, Medical Dictionary for Regulatory Activities; Rd, lenalidomide-dexamethasone; TEAE, treatment-emergent adverse event.

Supplemental Table 8. HRU during treatment in the intent-to-treat population

Healthcare resource	Ixazomib-Rd (N = 351)	Placebo-Rd (N = 354)
Hospitalizations*		
Number of patients with ≥1 hospitalization, n (%)	193 (55.0)	187 (52.8)
Number of hospitalizations, n	405	400
Number of hospitalizations per patient, mean (StD)	2.1 (1.78)	2.1 (1.72)
Rate of hospitalizations per patient-year, (95% CI)	0.332 (0.299-0.364)	0.309 (0.279-0.339)
Median length of time spent in hospital for patients with ≥1 hospitalization, days (range)	12.0 (1-700)	12.0 (1-377)
ER Stays		
Number of patients with ≥1 ER stay, n (%)	89 (25.4)	84 (23.7)
Number of ER stays	185	156
Number of ER stays per patient, mean (StD)	2.1 (2.10)	1.9 (1.68)
Rate of ER stays per patient-year (95% CI)	0.151 (0.130-0.173)	0.120 (0.102-0.139)

Outpatient Visits		
Number of patients with ≥1 outpatient visit, n (%)	271 (77.2)	269 (76.0)
Number of outpatient visits	5093	5581
Number of outpatient visits per patient, mean (StD)	18.8 (27.30)	20.7 (27.87)
Rate of outpatient visits per patient-year (95% CI)	4.171 (4.056-4.285)	4.310 (4.197-4.424)

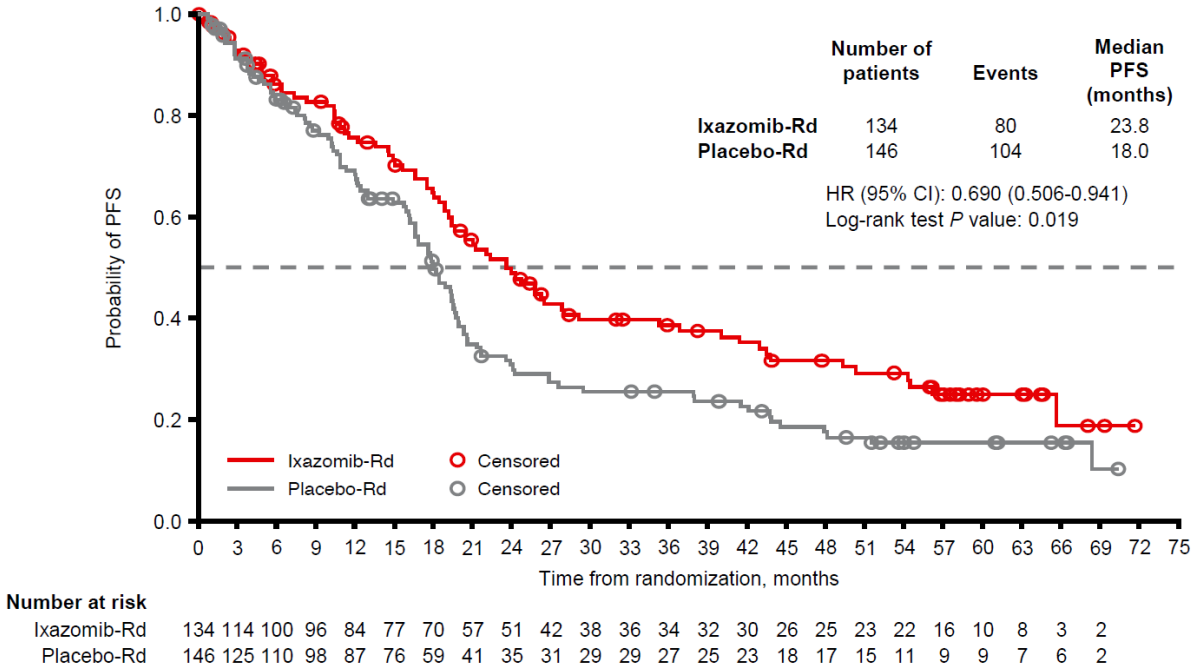
CI, confidence interval; ER, emergency room; HRU, healthcare resource utilization; Rd, lenalidomide-dexamethasone; StD, standard deviation.

*Defined as ≥1 overnight stay in an acute care unit, palliative care unit, hospice, or intensive care unit.

Supplemental Figure 1. Kaplan-Meier analysis of PFS of prespecified patient subgroups of (A) patients with expanded high-risk cytogenetic abnormalities, (B) patients <75 years old, (C) patients with creatinine clearance >60 mL/min.

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; Rd, lenalidomide-dexamethasone.

A)



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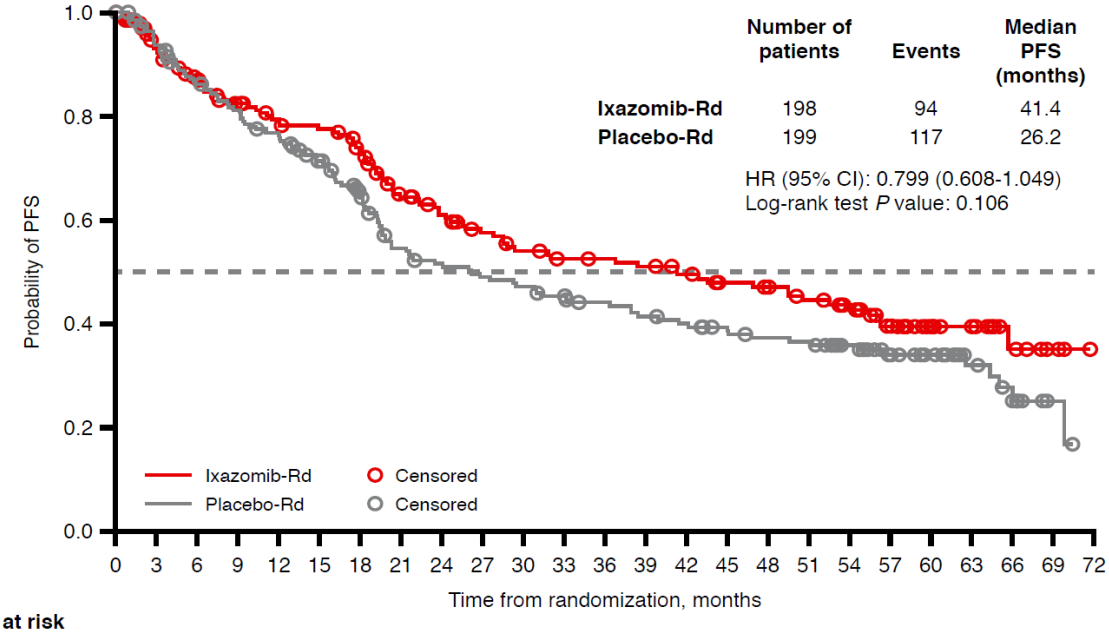
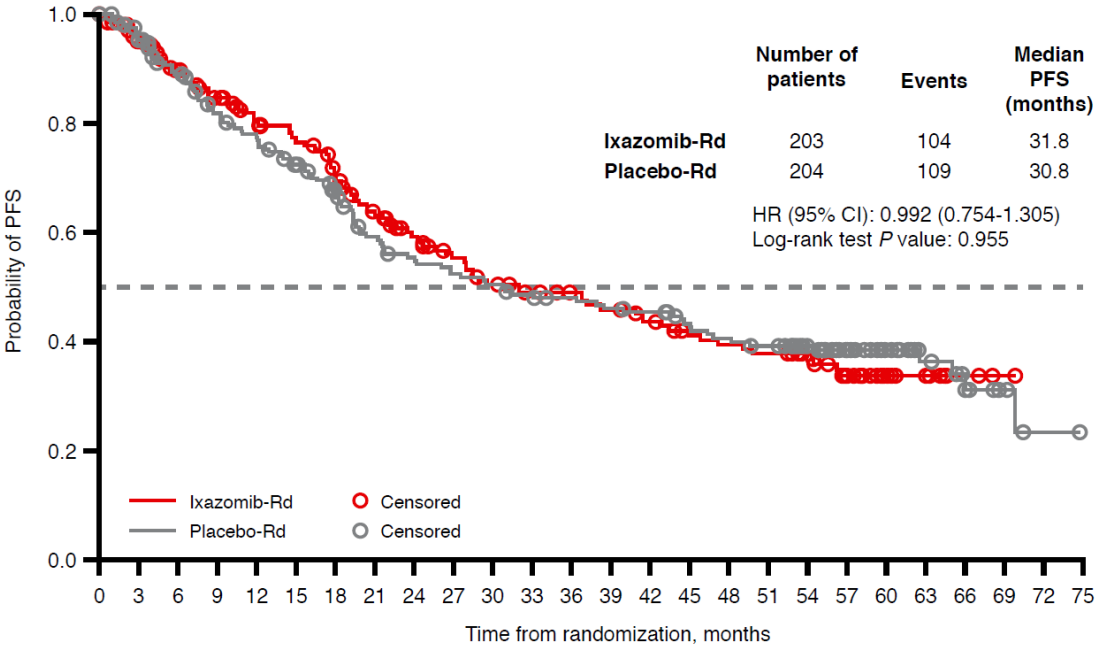


Number at risk

Ixazomib-Rd	198	170	154	140	132	128	117	98	90	81	75	71	70	68	64	59	57	52	46	35	23	17	8	3
Placebo-Rd	199	176	159	149	139	125	109	89	83	79	76	72	67	63	60	56	52	51	43	33	27	16	11	3

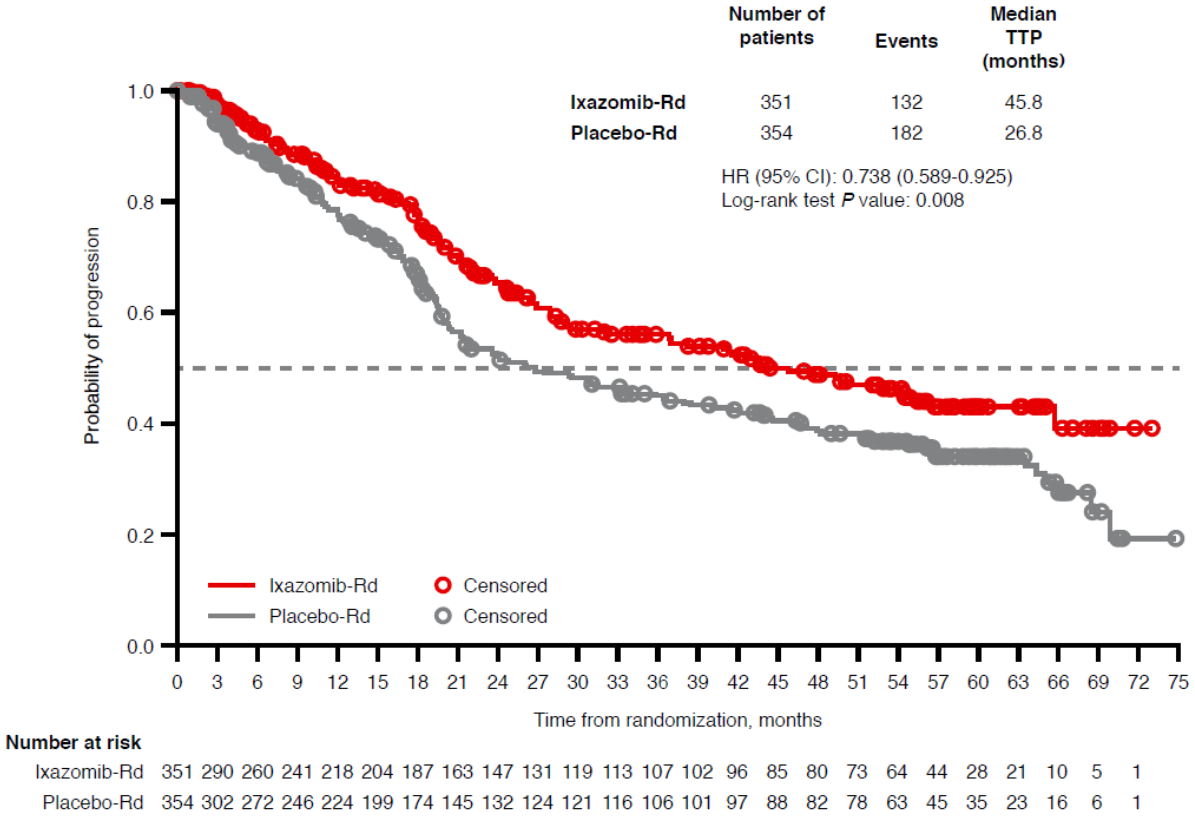
C)



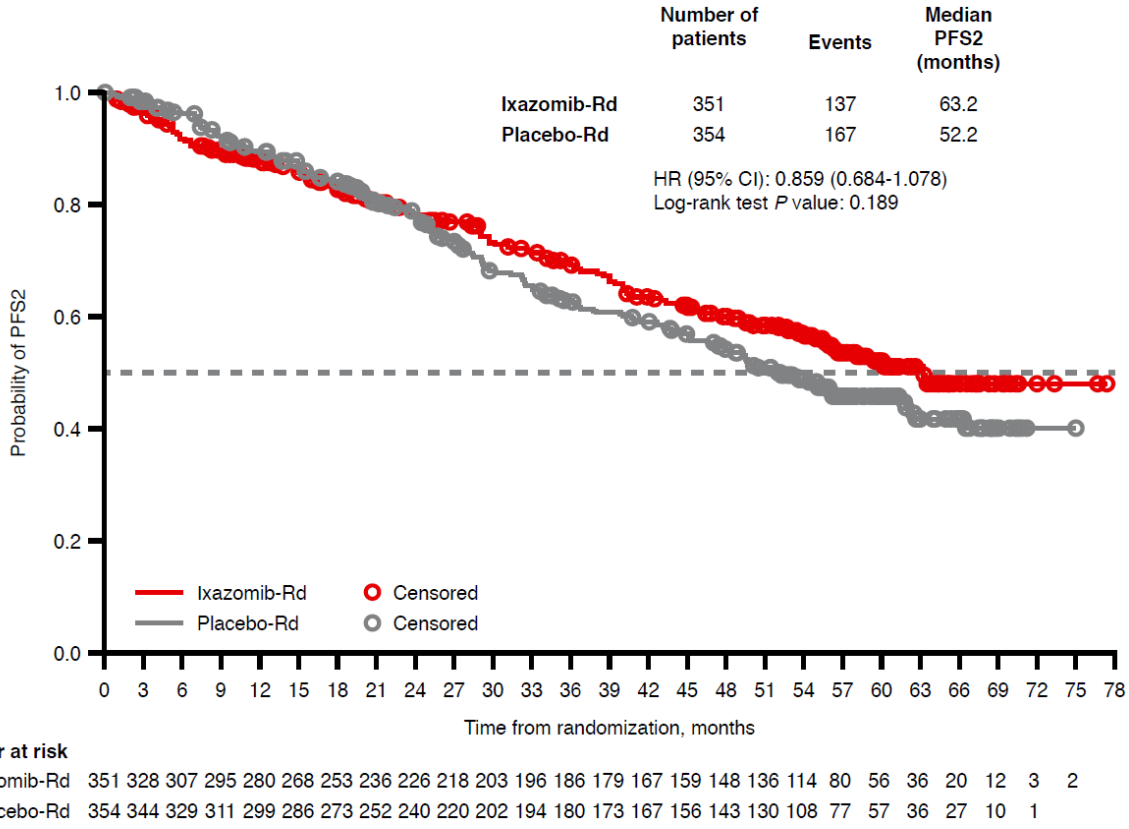
Number at risk

Ixazomib-Rd	203	184	165	151	138	130	117	101	90	80	72	67	64	60	55	50	47	45	39	30	16	13	4	1
Placebo-Rd	204	182	165	148	139	126	112	96	89	84	81	77	74	71	69	63	59	56	48	36	26	17	12	5	1

Supplemental Figure 2. Kaplan-Meier analysis of TTP by independent review on the intent-to-treat population. In patients aged <75 years (n=397), median TTP was 49.3 months with ixazomib-Rd and 30.9 months with placebo-Rd (HR, 0.767; 95% CI, 0.572-1.030). In patients aged ≥75 years (n=308), median TTP was 43.5 months with ixazomib-Rd and 23.6 months with placebo-Rd (HR, 0.697; 95% CI, 0.490-0.994). CI, confidence interval; HR, hazard ratio; Rd, lenalidomide-dexamethasone; TTP, time to progression.



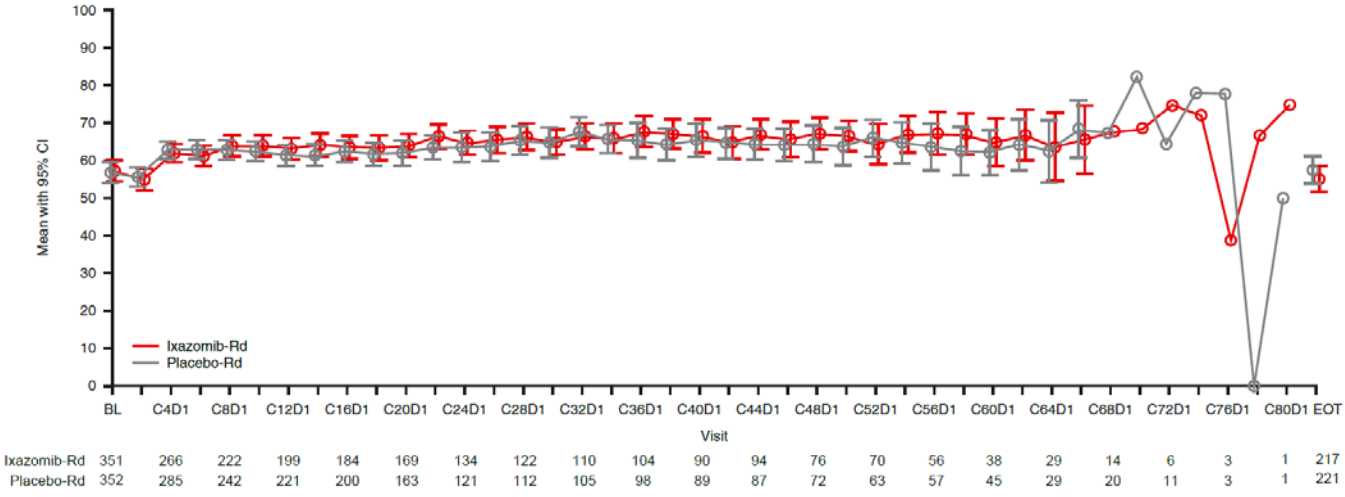
Supplemental Figure 3. Kaplan-Meier analysis of PFS2, defined as the date from randomization to the date of second disease progression, by independent review on the intent-to-treat population. CI, confidence interval; HR, hazard ratio; PFS2, progression-free survival 2; Rd, lenalidomide-dexamethasone.



Number at risk

Ixazomib-Rd	351	328	307	295	280	268	253	236	226	218	203	196	186	179	167	159	148	136	114	80	56	36	20	12	3	2
Placebo-Rd	354	344	329	311	299	286	273	252	240	220	202	194	180	173	167	156	143	130	108	77	57	36	27	10	1	

Supplemental Figure 4. Mean EORTC QLQ-C30 global health status/QoL score over time. BL, baseline; C, cycle; CI, confidence interval; D, day; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; EOT, end of treatment; QoL, quality of life.



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Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

CLINICAL STUDY PROTOCOL C16014 AMENDMENT 4

MLN9708

A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Newly Diagnosed Multiple Myeloma

Protocol Number:	C16014
Indication:	Newly Diagnosed Multiple Myeloma
Phase:	3
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2013-000326-54
IFM Number	IFM 2013-07
Therapeutic Area:	Oncology

Protocol History

Original	14 February 2013
Amendment 1	22 July 2014
Amendment 1A (for use in South Korea continuation only)	02 February 2016
Amendment 2	30 November 2016
Amendment 2A (for use in South Korea continuation only)	14 March 2017
Amendment 3	10 May 2017
Amendment 4 (substantial)	09 August 2019

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PPD

Rationale for Amendment 4

This document describes the changes in reference to the protocol incorporating Amendment No. 4. The primary reason for this amendment is to modify the statistical analysis plan to ensure timely analysis of the primary endpoint, progression-free survival (PFS), in light of the slower than expected PFS event rate over the past year. The second interim analysis (IA) – the final analysis for PFS – will now take place when approximately 370 PFS events have been observed. Power remains sufficient at 92%.

Additionally, this amendment clarifies other elements of the study design and procedures. REVLIMID or generic lenalidomide may be administered as part of the study treatment regimen [redacted]. The requirement to document adverse events that require breaking the blind in the electronic case report form (eCRF) has been removed. The serious adverse event (SAE) reporting contact information in Japan has been updated from [redacted] to [redacted]. The duration of new primary malignancy adverse event (AE) assessment has additionally been clarified.

Minor grammatical, editorial, formatting, and administrative changes are included for clarification purposes only. For specific examples of changes in text and where the changes are located, see Section 15.17.

Changes in Amendment 4

1. [redacted]
2. Update statistical procedures to modify the number of events for the final PFS analysis.
3. Clarify the statistical boundary for PFS at the second IA.
4. Clarify that REVLIMID or generic lenalidomide may be administered as part of the study treatment regimen.
5. Remove the requirement to document adverse events that require breaking the blind in the eCRF.
6. Update the SAE reporting contact information in Japan [redacted]
7. Clarify the duration of new primary malignancy AE assessment.
8. Clarify the locations of study centers.

PROTOCOL SUMMARY

Study Title: A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Newly Diagnosed Multiple Myeloma

Study Phase: 3

Number of Patients: Approximately 701

Study Objectives

Primary Objective:

- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves progression-free survival (PFS) in patients with newly-diagnosed multiple myeloma (NDMM)

Key Secondary Objectives:

- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves overall survival (OS)
- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves the rate of complete response (CR)
- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves pain response rate, as assessed by the Brief Pain Inventory – Short Form (BPI-SF) and analgesic use

Other Secondary Objectives:

- To determine overall response rate (ORR), including partial response (PR), very good partial response (VGPR), and CR
- To determine time to response (TTR), duration of response (DOR), and time to progression (TTP)
- To determine the effect of the addition of MLN9708 to lenalidomide and dexamethasone on progression-free survival 2 (PFS2), defined as the date from randomization to the date of second disease progression or death from any cause, whichever comes first
- To determine the safety of the addition of MLN9708 to lenalidomide and dexamethasone
- To assess change in global health status, as measured by the global health status, functioning, and symptoms as measured by the patient-reported outcome (PRO) instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and MY-20 module
- To determine the PFS and OS in high-risk cytogenetic patient groups defined by the following cytogenetic abnormalities: t(4;14), t(14;16), amp(1q21), and del(17p)
- To evaluate minimal residual disease status (MRD), via flow cytometry, in patients suspected to have reached CR at any time during the entire conduct of the study, and at Cycle 18 for patients who have maintained CR until that point. The impact of MRD status on TTP, PFS, and OS will be assessed.

- To assess time to pain progression
- To collect pharmacokinetic (PK) data to contribute to population PK analyses
- To evaluate the frequency of skeletal-related events (SREs) (eg, new fractures [including vertebral compression fractures]), irradiation of or surgery on bone, or spinal cord compression) from baseline through the last survival assessment

CCI

[redacted]

Overview of Study Design:

This is a phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of MLN9708 versus placebo when added to lenalidomide and dexamethasone (LenDex) in patients with NDMM. Adult patients with a confirmed diagnosis of symptomatic multiple myeloma (MM) who have not received previous antimyeloma treatment, who are ineligible for high-dose therapy plus stem cell transplantation (HDT-SCT) because of age (ie, ≥ 65 years) or coexisting conditions per investigator judgment, who are candidates for treatment with LenDex as their standard therapy, and who meet other eligibility criteria detailed in Section 5 will be enrolled in this study.

Following the Screening period, patients to be enrolled will be randomized to receive either MLN9708 or placebo in a double-blind fashion in addition to the background therapy of LenDex. Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms, stratified by age

(< 75 years vs ≥ 75), International Staging System (ISS) (stage 1 or 2 vs stage 3), and BPI-SF worst pain score (< 4 vs ≥ 4) at screening.

Patients will receive oral MLN9708 4.0 mg or a matching placebo capsule on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients over 75 years of age at randomization will receive a reduced dexamethasone dose (20 mg). Dose modifications may be made throughout the study based on toxicities. Patients with a low creatinine clearance ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) but ≥ 30 mL/min will receive a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

Patients may continue to receive treatment as outlined previously for 18 cycles (approximately 18 months), or until progressive disease (PD) or unacceptable toxicity, whichever comes first. After 18 cycles, patients will continue treatment in the same randomization arm on the same schedule with modified dose levels of the study drug and lenalidomide: reduce MLN9708 (or placebo) dose to 3.0 mg, reduce lenalidomide dose to 10 mg, and no dexamethasone.

The treatment period of the study is defined as any time a patient is receiving any of the study drug regimen, and will be comprised of 28-day treatment cycles. Patients will be seen at regular treatment cycle intervals while they are participating in the study: weekly for the first 2 cycles, twice a treatment cycle during the third cycle, and then once a treatment cycle for the remainder of their participation in the treatment period, until they experience disease progression or discontinue for alternate reasons. If a patient discontinues treatment with the study regimen before disease progression, they will enter the PFS follow-up period of the study.

Patients will be assessed for disease response and progression by the investigator and an independent review committee (IRC). Response will be assessed according to the International Myeloma Working Group (IMWG) criteria for all patients every cycle during the treatment period until PFS significance has been claimed in this study. After the primary endpoint has been met, central efficacy and investigator assessments for protocol purposes will be discontinued except for investigator assessment of PFS2. For patients who discontinue treatment before disease progression, assessments will be made every 4 weeks during the PFS follow-up period until disease progression is confirmed or the patient is started on another anticancer therapy, or the PFS significance has been claimed in this study. After disease progression or start of another anticancer therapy, all patients will be followed for survival in the OS follow-up period. Patients will be contacted every 12 weeks from the start of the OS follow-up period until death or termination of the study by the sponsor. All subsequent anticancer therapies for MM will be reported as part of the OS follow-up period assessments. In addition, patients who receive a subsequent anticancer therapy for MM will be assessed by the investigator for disease response (at minimum disease progression) on the second line of anticancer therapy to determine PFS2.

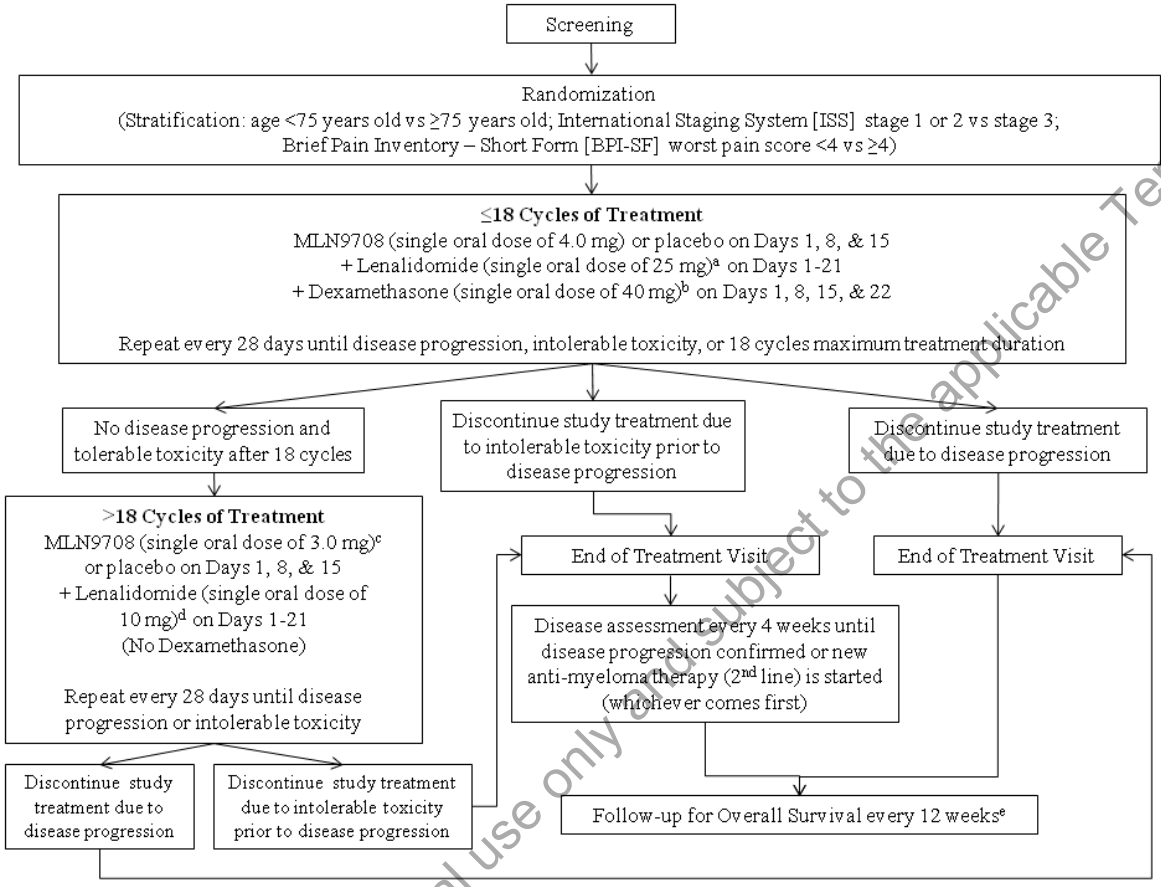
Study Population:

Adult patients with a confirmed diagnosis of symptomatic MM, who have not received previous antimyeloma treatment, who are not transplant eligible, and who are candidates for treatment with LenDex will be enrolled in this study.

Duration of Study:

The duration of the study, including enrollment, treatment, and follow-up, will be approximately 87 months, including a 27-month enrollment period and an additional 60-month (5-year) follow-up from the last patient enrolled.

STUDY OVERVIEW DIAGRAM



a Patients with a low creatinine clearance of ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) but ≥ 30 mL/min will receive a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

b Patients over 75 years of age at randomization will receive a reduced dexamethasone dose (20 mg).

c If the dose of MLN9708 (or placebo) was reduced to 3.0 or 2.3 mg during the first 18 cycles of treatment, dose will remain at that reduced level beyond 18 cycles (see Table 4-1).

d If the dose of lenalidomide was reduced to 15 mg or 10 mg during the first 18 cycles of treatment, dose will be 10 mg beyond 18 cycles. If the lenalidomide dose was reduced to 5 mg during the first 18 cycles of treatment, dose will remain at 5 mg beyond 18 cycles (see Table 4-1).

e Patients who receive a subsequent line of anticancer therapy will be evaluated by the investigator for disease response (at minimum disease progression) for determination of PFS2. Disease response on the next line of therapy will be recorded every 12 weeks during the OS follow-up period until PFS2 is reported or a new (third) line of anticancer therapy is started, whichever comes first.

SCHEDULE OF EVENTS

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond		Every 4 weeks	Every 12 weeks
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1			
Window		± 2 days												+1 wk	± 1 wk	± 1 wk
Informed Consent	X[b]															
Inclusion/Exclusion Criteria[c]	X															
Demographics	X															
Complete Medical History and Disease Staging	X															
Complete Physical Exam	X													X		
Symptom-Directed Physical Exam		X				X				X		X	X		X	
ECOG Performance Status	X					X				X		X	X	X	X	
Vital Signs	X	X				X				X		X	X	X	X	
Height (cm)	X															
Weight (kg)	X					X				X		X[d]	X[d]	X	X	
Pregnancy Test[e]	X	X	X	X	X	X				X		X	X	X		
12-lead ECG	X													X		
Hematology Panel[f]	X	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X	X	X	X		
Chemistry Panel[f]	X	X				X				X		X	X	X		
Thyroid Function Testing	X											X[h]	X[h]	X		
Urinalysis	X															
EORTC-QLQ-C30 and MY-20[i]	X	X				X						X[j]	X[j]	X	X	
EQ-5D[i]	X	X				X				X		X	X	X	X	X[k]

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond		Every 4 weeks	Every 12 weeks
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1			
Window		± 2 days												+1 wk	± 1 wk	± 1 wk
Pain Assessment: BPI-SF & 24-hour analgesic form (also for unscheduled visit)[i]	X	X				X				X		X	X	X	X	
CCI																
Bone Mineral Density (DEXA) scan	X[l]											X[l]	X[l]		X[l]	
Skeletal Survey	X												X[m]		X[m]	
Radiographic Disease Assessment[n]	X					X						X	X	X	X	
β2-microglobulin	X															
M-protein Measurements (SPEP)[p]	X	X[o]				X				X		X	X	X	X	
M-protein Measurements (UPEP [24hr Urine collection])[p]	X	X[o]				X				X		X	X	X	X	
Serum Free Light Chain Assay[p]	X	X[o]				X				X		X	X	X	X	
Immunofixation - serum and urine[p]	X	X[o]				X				X		X	X	X	X	
Quantification of Ig[q]	X	X[o]				X				X		X	X	X	X	
Bone Marrow Aspiration																
Disease Assessment	X[r]					X[r]				X[r]		X[r]	X[r]	X[r]	X[r]	
Molecular Analysis and Cytogenetics	X[s, t]													X[s]		

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond		Every 4 weeks	Every 12 weeks
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1			
Window		± 2 days												+1 wk	± 1 wk	± 1 wk
Minimal Residual Disease		To be done at any time if CR is suspected[u]											X[u]			
Blood Samples for Biomarker Analysis																
CCI [redacted]																
Adverse Event Reporting		Recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen[w]														
		Serious adverse events and serious pretreatment events will be collected from signing of the informed consent form through 30 days after the last dose of drug in the study drug regimen														
Concomitant Medications/Procedures		Recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen														
Skeletal-related Events		Continuous from the start of study drug regimen administration until death or termination of the study by the sponsor														
Narcotic and Other Analgesic Use		Recorded from the first dose of study drug regimen until confirmed progressive disease														
New Primary Malignancy Reporting		Continuous from the start of study drug regimen administration until death or termination of the study by the sponsor														
Subsequent Therapy/ Disease Status[x]																X
Survival																X

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond		Every 4 weeks	Every 12 weeks
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1			
Window		± 2 days												+1 wk	± 1 wk	± 1 wk
Study Drug Regimen Administration[y]																
MLN9708/Placebo		Days 1, 8, and 15 of each cycle														
Lenalidomide		Continuous Days 1-21 of each cycle														
Dexamethasone		Days 1, 8, 15, and 22 of each cycle														

Abbreviations: D = study day; del = deletion; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PFS = progression-free survival; SPEP = serum protein electrophoresis; t = translocation; UPEP = urine protein electrophoresis; wk = week;

Tests and procedures should be performed on schedule, but occasional changes may be allowed (± 2 days or a longer window after discussion with the Millennium project clinician or designee) for holidays, vacations, and other administrative reasons. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed prior to dosing.

a Quality Review by MPI/designee clinician required prior to discontinuing patient from treatment for progressive disease. A treatment discontinuation form must be submitted and approved prior to removing a patient from study treatment for disease progression, toxicity, or any other reason.

b Informed consent may be obtained before the 28-day Screening period and must be documented before initiating any screening procedures.

c Confirmation of patient eligibility by MPI/designee clinician required prior to randomization.

d Weight to be taken Day 1 of each cycle.

e Pregnancy tests:

- Screening for all countries except Canada: Females of childbearing potential (FCBP) are required to have TWO medically supervised negative pregnancy tests (serum or urine with sensitivity of at least 25 mIU/mL), even if continuous abstinence is the chosen method of contraception, prior to the first dose of lenalidomide. One test must be obtained within 10-14 days and the other test must be obtained within 24 hours prior to the start of the study drug regimen at Cycle 1, Day 1.
- Screening for Canada: FCBP are required to have TWO medically supervised negative serum pregnancy tests with sensitivity of at least 25 mIU/mL, even if continuous abstinence is the chosen method of contraception, prior to the first dose of lenalidomide. One test must be obtained within 7–14 days and the other test within 24 hours prior to the start of the study drug regimen at Cycle 1, Day 1.
- On Treatment: Pregnancy tests for FCBP to be collected weekly during Cycle 1 and then within 24 hours of beginning each subsequent cycle. Lenalidomide package insert must be followed while patients remain on therapy. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on therapy. For Canada: all pregnancy tests must be performed using serum with a sensitivity of at least 25 mIU/mL.

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond		Every 4 weeks	Every 12 weeks
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1			
Window		± 2 days												+1 wk	± 1 wk	± 1 wk

- End of Treatment: Pregnancy for FCBP to be collected at treatment discontinuation and at Day 28 following drug discontinuation (± 1 wk window for other end of treatment assessments does NOT apply). If menstrual cycles are irregular, the pregnancy testing must occur at drug discontinuation and at Days 14 and 28 following drug discontinuation. For Canada: all pregnancy tests must be performed using serum with a sensitivity of at least 25 mIU/mL.

f Clinical laboratory evaluations will be performed by a central laboratory. For on study treatment dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must still be sent to the central laboratory in parallel. The central laboratory results will be used for determination of eligibility criteria. Patients may have central laboratory assessments repeated when discrepant results between the central and local laboratories are observed. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Days 8, 15, and 22 dosing, where required. Local laboratory evaluations may be done more frequently at the investigators discretion, ie for acute management of treatment-emergent adverse events.

g Patients who live a far distance from the study center or who have other logistical difficulties may have the Cycles 1 and 2, Days 7 and 21 CBC blood draw done by a local laboratory, upon consultation and approval with the investigator.

h Thyroid function testing required every 4 cycles on treatment.

i CCI [redacted].

j Required every other cycle after Cycle 2 (ie, Cycles 1, 2, 4, 6, etc.) during the treatment period.

k During the OS follow-up, assessments can be made over the phone and do not require a clinic visit.

l Dual-energy X-ray absorptiometry (DEXA) scans will be done of the lumbar spine and femoral neck at screening (the DEXA scan does not need to be repeated if already performed within 8 weeks of randomization), 6 months, 1 year, and then annually until progressive disease (±4 weeks at the corresponding study visit to approximately 6 or every 12 months of treatment).

m Skeletal survey will be performed at screening (within 8 weeks prior to randomization) and a minimum of every 12 months from randomization until disease progression for all patients. More frequent radiological assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions).

n Patients with documented extramedullary disease must have radiographic disease assessments (CT/PET-CT/MRI) performed at screening, every other cycle during treatment until PD, and every 8 weeks during the PFS follow-up period until PD for patients who permanently discontinue study drug regimen before PD. Modality should be kept consistent throughout. Screening evaluations may be performed within 8 weeks prior to randomization.

o If the screening test was performed more than 14 days prior to the first dose, the test will be repeated at baseline.

p SPEP, UPEP, serum free light chain assay, and immunofixation to be done on Day 1 of every cycle and at the End of Treatment visit until PFS significance has been claimed for this study. At that time, central efficacy and investigator assessments for protocol purposes will be stopped and not recorded in the eCRF, except for investigator assessment of PFS2. For patients who discontinue study treatment prior to PD, assessments will be done every 4 weeks during the PFS follow-up period until PD, the start of another anticancer therapy, or PFS significance has been claimed for this study.

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond		Every 4 weeks	Every 12 weeks
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1			
Window		± 2 days												+1 wk	± 1 wk	± 1 wk

q Blood samples for quantification of immunoglobulins (IgM, IgG, IgA) will be obtained throughout the study at the time points specified until PFS significance has been claimed for this study. Quantitative IgD and IgE will be done at screening (and baseline if needed) only. For the rare patient with IgD or IgE multiple myeloma, the quantitative test for that antibody will be followed at the same time points as quantitative Igs (in addition to IgM, IgG, and IgA).

r To be performed at local lab to assess disease status within 8 weeks of randomization. Only to be repeated if patient is considered to possibly have resolution of serum and urine M-protein consistent with CR or to investigate suspected PD if applicable.

s Bone marrow aspirate (first or second pull preferred) for molecular analysis and cytogenetics are required to be collected and sent to the central lab within 8 weeks of randomization. An additional bone marrow aspirate at relapse, only for patients who initially respond and then relapse, should be collected. This additional sample is optional, but highly recommended.

t Additional cytogenetics may also be done locally (optional) if the site has the capability to perform analysis and sufficient specimen available. Assessment of the following should be obtained if possible: amp(1q21), translocations t(4;14) and t(14;16), and del(17p).

u Bone marrow aspirate to be collected for assessment of MRD in all patients suspected to have reached CR anytime during the entire conduct of the study. In addition, a repeat bone marrow aspirate for MRD assessment will be collected at Cycle 18 for only the patients who have maintained a CR until that point (this sample can be collected up to 4 weeks after Cycle 18). If a patient has had MRD testing because of a suspected CR within 2 cycles of Cycle 18, then this repeat MRD assessment does not need to be performed. Samples are required to be sent to central lab for analysis.

v CCI [redacted]

w If peripheral neuropathy is present at baseline, the Common Toxicity Criteria for Adverse Events (CTCAE) grade must be reported in the patient's medical history. When PN occurs during active treatment on study, each subsequent monthly evaluation will record the CTCAE grade of peripheral neuropathy at that visit. (This is in contrast to other AEs where only increases in grade are recorded until the maximum grade is reached and then followed at that grade until complete resolution or return to baseline.) Peripheral neuropathy will be followed every 4 weeks until 1) resolution of peripheral neuropathy, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after disease progression has occurred, whichever occurs first.

x All subsequent anticancer therapies for MM will be reported every 12 weeks. Patients who receive a subsequent anticancer therapy for MM will be assessed by the investigator for disease response (at minimum disease progression) to determine PFS2; response assessments should be made using local laboratory results, and the frequency will be determined by the investigator (recommended every 12 weeks) on the next line of therapy only. When a patient experiences disease progression on the next line of anticancer therapy or initiates a subsequent line of anticancer therapy, whichever comes first, further disease response will no longer be recorded.

y The study drug regimen must be initiated within 5 days of randomization on study.

MLN9708 Pharmacokinetic Sampling Schedule

Cycle 1			Cycle 2-3		Cycles 4-12
Day 1		Day 14	Day 1	Day 14	Day 1
Postdose 1 hour (± 0.25)	Postdose 4 hour (± 0.75)	Predose[a,b]	Predose[b,c]	Predose[a,b]	Predose[b,c]
X	X	X	X	X	X

a If PK sample is taken on a dosing day (due to allowable ± 2-day window of visits), PK sample must be taken within 2 hours prior to dose of any study drug. If PK sample is taken on a non-dosing day, ie, sample on Day 14 and dose on Day 15, PK sample can be taken at any time during the visit.

b If a predose sample is drawn from a patient and the patient does not receive a dose on that protocol visit day, a second predose sample does not need to be drawn on the subsequent visit where the dose is administered. All future distinctive visits should be done as per the protocol.

c Day 1 predose PK assessments should occur within 4 hours of dosing.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
AL	systemic light chain
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCRP	breast cancer resistance protein
BPI-SF	Brief Pain Inventory – Short Form
BRAF	gene/gene product: human homolog of a murine sarcoma viral oncogene

Abbreviation	Term
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CHW	Cui-Hung-Wang
CL	clearance
C_{max}	maximum (peak) concentration
CMH	Cochran-Mantel-Haenszel
CO_2	carbon dioxide
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction(s)
DEXA	dual-energy X-ray absorptiometry
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment (visit)
EQ-5D	EuroQol 5-Dimensional Health Questionnaire
EQ VAS	EQ visual analogue scale
ESMO	European Society for Medical Oncology
FA	final analysis
FCBP	female of childbearing potential
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor

Abbreviation	Term
HDT-ASCT	high-dose therapy followed by autologous stem-cell transplantation
HIV	human immunodeficiency virus
CC[redacted]	[redacted]
IA	interim analysis
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IFM	Intergroupe Francophone du Myelome
IG	immunoglobulin
CCI[redacted]	[redacted]
IMiD	immunomodulating drugs
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IMWG	International Myeloma Working Group
IR	immunophenotypic response
IRB	institutional review board
IRC	independent review committee
ISC	independent statistical center
ISS	International Staging System
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous; intravenously
IXRS	interactive voice/ web response system
K-M	Kaplan Meier
KRAS	gene/gene product: Kirsten rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
LenDex	lenalidomide + dexamethasone
LMWH	low molecular weight heparin
LOCF	last observation carried forward
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference

Abbreviation	Term
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MP	melphalan + prednisone
MPI	Millennium Pharmaceuticals, Inc.
MPR	melphalan + prednisone + Revlimid (lenalidomide)
MPR-R	melphalan + prednisone + Revlimid (lenalidomide) with Revlimid as maintenance
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRP2	multidrug resistance associated protein
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
CCI	[redacted]
CCI	[redacted]
NSAID	non-steroidal anti-inflammatory drug
OME	oral morphine equivalent
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PFS2	progression-free survival 2 (from randomization on study to PFS on the next line of treatment)
P-gp	P-glycoprotein
PI	package insert
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	*per os*; by mouth (orally)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PR	partial remission ***or*** partial response
PRO	patient-reported outcome(s)

Abbreviation	Term
CCI	[redacted]
QD	*quaque die*; each day; once daily
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RD	Revlimid (lenalidomide) + dexamethasone
RRAL	relapsed and/or refractory systemic light chain amyloidosis
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SCT	stem cell transplant
SD	stable disease
SmPC	Summary of Product Characteristics
SPEP	serum protein electrophoresis
SRE	skeletal-related event
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum (peak) concentration
CCI	[redacted]
TTP	time to (disease) progression
TTR	time to response
TW	twice weekly
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
US	United States
V2	volume of distribution in the central compartment
VGPR	very good partial response
VMP	VELCADE (bortezomib) + melphalan + prednisone
VRD	VELCADE (bortezomib) + Revlimid (lenalidomide) + dexamethasone
WHO	World Health Organization

Study Period Definitions

Screening Period	A period of time 1 to 28 days before randomization when a prospective patient is screened for eligibility criteria.
Treatment Period	The time during which a patient receives any dose of the study drug regimen, and is comprised of 28-day treatment cycles.
End of Treatment (EOT) Visit	A visit within 30 days after the last dose of the study drug regimen when certain procedures are performed, as outlined in the Schedule of Events.
Progression-free Survival Follow-up Period	Visits for patients who stop treatment with the study drug regimen for any reason other than progressive disease. See the Schedule of Events for appropriate assessments. The progression-free survival follow-up should occur every 4 weeks until the occurrence of disease progression; radiographic disease assessments are to be performed every 8 weeks for patients with documented extramedullary disease.
Progression-free Survival 2 Follow-up Period	Patients who receive a subsequent anticancer therapy for MM will be assessed by the investigator for disease response (at minimum disease progression) to determine PFS2; response assessments should be made using local laboratory results, and the frequency will be determined by the investigator (recommended every 12 weeks) on the next line of therapy only (as part of the overall survival follow-up period [see below]). When a patient experiences disease progression on the next line of anticancer therapy or initiates a third line of anticancer therapy, whichever comes first, further disease response will no longer be recorded.
Overall Survival Follow-up Period	Visits (may be conducted by phone, internet, etc) every 12 weeks to assess survival. Depending on response to treatment, patients may enter the OS follow-up period at different times: • Patients who experience disease progression during the treatment period enter the OS follow-up period after the EOT visit • Patients who do not experience disease progression during the treatment period go on to the PFS follow-up period. They will enter the OS follow-up after experiencing disease progression in the PFS follow-up. • Patients who are removed from study treatment prior to disease progression (ie, for toxicity) AND immediately continue to receive a subsequent line of anticancer therapy will skip the PFS follow-up period and enter the OS follow-up period.

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Multiple myeloma (MM), a B-cell tumor of malignant plasma cells within the bone marrow, remains incurable despite advances in novel therapies with proteasome inhibitors, immunomodulating drugs (IMiD), and stem cell transplant (SCT) therapy. MM is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and can result in bone marrow failure, bone destruction, hypercalcemia, and renal failure. It constitutes approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide.[1] In the Americas, Canada, and Western European countries, approximately 5 to 7 new cases of MM are diagnosed per 100,000 people each year.[1-3] Although less common in Asian countries, incidences of MM have increased almost 4-fold in the past 25 years and are characterized by younger onset age, more invasive disease, and a less favorable prognosis.[4,5]

MM is sensitive to many cytotoxic drugs including alkylating agents, anthracyclines, and corticosteroids for both initial treatment and relapsed disease. Over the past decade, significant achievements have been made in expanding treatment options for MM with novel therapies such as thalidomide, bortezomib, and lenalidomide. These regimens have extended progression-free survival (PFS) and/or time-to-progression (TTP).[6-10] The introduction of novel therapies and the increased use of high-dose therapy significantly improved overall survival in patients with newly diagnosed myeloma who were eligible for autologous stem cell transplant (ASCT).[11-13] For patients with newly diagnosed myeloma who are not eligible for ASCT, adding VELCADE to melphalan and prednisone (VMP) significantly extended overall survival. Final results of the international, multicenter, phase 3 VISTA trial confirmed that after 5 years of follow-up, VMP demonstrated a persistent, significant overall survival (OS) benefit versus melphalan and prednisone (MP) with a 13.3 median month increase (43.1 vs 56.4 mo, HR 0.695, p = 0.0004).[14] Palumbo reported that adding Revlimid onto MP (MPR) and with Revlimid as maintenance (MPR-R), significantly improved PFS in newly diagnosed myeloma patients who were ineligible for ASCT; the median PFS was significantly longer with MPR-R (31 months) than with MPR (14 months; hazard ratio, 0.49; $p < 0.001$) or MP (13 months; hazard ratio, 0.40; $p < 0.001$).[15]

Despite more therapeutic options, MM remains incurable, and there is a need for new and better agents. Patients who relapse after their initial therapy demonstrate variable responses to subsequent treatments with decreasing likelihood and duration of response (DOR). Patients become refractory to approved therapies and ultimately are left with no alternative treatment options. In an effort to expand the therapeutic armamentarium against MM with agents that target the proteasome, Millennium Pharmaceuticals, Inc. (Millennium) has developed MLN9708, a small molecule 20S proteasome inhibitor.

1.1.2 MLN9708, Millennium's Next-Generation Proteasome Inhibitor

The proteasome was validated as an effective oncology target with the clinical success of intravenous and subcutaneous bortezomib (VELCADE®), the first-in-class, small molecule proteasome inhibitor developed by Millennium. Building on the efficacy seen with bortezomib in MM and other hematologic malignancies, Millennium has subsequently developed oral MLN9708 to improve the pharmacology of the agent and provide a more convenient mode of drug administration.

Like VELCADE, MLN9708 is a modified peptide boronic acid. MLN9708 is the citrate ester of MLN2238, the biologically active form that potently, reversibly, and selectively inhibits the proteasome. MLN9708 was formulated to improve the chemical properties of MLN2238 for clinical delivery. MLN9708 rapidly hydrolyzes to MLN2238 upon contact with either plasma or aqueous solutions. In contrast to bortezomib, MLN9708 demonstrates a faster dissociation rate from the proteasome, possibly resulting in enhanced tumor penetration, exhibits antitumor activity in a broader range of tumor xenografts, and has more prolonged tissue penetration.

MLN2238 preferentially binds the β5 site of the 20S proteasome with a concentration producing 50% inhibition (IC_{50}) of 3.4 nM. At higher concentrations, it also inhibits the activity of the β1 and β2 sites. MLN2238 was selective for the proteasome when tested against a panel of proteases (IC_{50} values between 20 and 100 μM), kinases (IC_{50} values > 10 μM), and receptors (IC_{50} values > 10 μM). MLN2238 and bortezomib have different β5 proteasome dissociation half-lives ($t_{1/2}$), reflecting differences in their on-off binding kinetics (the β5 proteasome dissociation [$t_{1/2}$] for MLN9708 and bortezomib is 18 and 110 minutes, respectively). Based on these favorable characteristics, MLN9708 is anticipated to be effective against MM.

1.2 Nonclinical Experience

Detailed information regarding the nonclinical pharmacology, absorption, distribution, metabolism, excretion, pharmacokinetics (PK) and toxicology of MLN9708 may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

MLN9708 is the first investigational oral proteasome inhibitor in clinical trials in humans with safety, tolerability, PK, pharmacodynamics, and disease response assessed in each phase 1 and phase 1/2 study. As of 30 April 2012, 382 patients have been treated with MLN9708 across 9 enrolling sponsor-led phase 1 or phase 1/2 studies with a twice-weekly (TW) and a weekly dosing schedule being evaluated. MLN9708 is available as an intravenous and oral formulation. Regardless of the route of administration in the TW 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.

To date, the development of oral MLN9708 has focused on multiple myeloma (relapsed and/or refractory as well as newly diagnosed) and a different yet related plasma cell dyscrasia, systemic light chain (AL) amyloidosis. A clinical pharmacology study looking at drug-drug interactions, food effect, and bioavailability also uses the oral formulation. Additionally, patients with nonhematologic malignancies (Study C16001) and patients with advanced lymphoma (Study C16002) have been treated with the intravenous (IV) formulation of MLN9708.

1.3.1 Clinical Trial Experience Using the IV Formulation of MLN9708

There are 2 ongoing studies investigating IV MLN9708 in patients with advanced solid tumors and advanced lymphomas, a total of 140 patients have been treated in these studies as of 30 April 2012. These patients have been treated with different doses of MLN9708 as a single-agent treatment. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-1.

Table 1-1 Clinical Trials Using Intravenous MLN9708

Trial/ Population	Description	Doses Investigated
C16001 Solid tumors N = 116	IV, TW, single agent	0.125 to 2.34 mg/m^2 MTD: 1.76 mg/m^2 DLT: rash, thrombocytopenia, acute renal failure Enrollment closed
C16002 Lymphoma N = 24	IV, W, single agent	0.125 to 3.11mg/m^2 MTD: TBD DLT: neutropenia

Abbreviations: DLT = dose-limiting toxicity; IV = intravenous; MTD = maximum tolerated dose; TBD = to be determined; TW = twice weekly; W = weekly.

1.3.2 Clinical Trial Experience Using the Oral Formulation of MLN9708

In the 7 studies actively enrolling patients to investigate oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 either as a single-agent treatment (in 146 patients) or in combination with currently clinically available treatments (in 96 patients). Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-2.

Table 1-2 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 58	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia
C16004 RRMM N = 52	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, relevant to 2.23mg/m^2) Closed to enrollment

Table 1-2 Ongoing Studies of Oral MLN9708

C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer
C16007 RRAL N = 14	PO, W, single agent	4-5.5-mg fixed dose[a] W MTD: 4 mg DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest
C16008 NDMM N = 11	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] W MTD: TBD
C16009 Solid tumors, Lymphomas N = 22	PO, W, single agent	5.5-mg fixed dose[a] W

Abbreviations: BSA = body surface area; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RP2D= recommended phase 2 dose; RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; RRMM = relapsed and/or refractory multiple myeloma; TBD = to be determined; TW = twice weekly; W = weekly.

a Approximate 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.

Further details on planned and ongoing studies are provided in the IB.

1.4 Pharmacokinetics and Drug Metabolism

Clinical IV and oral 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. 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. 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 MLN2238, with negligible urinary excretion of the parent drug (< 5% of dose). In vitro studies indicate that MLN2238 is metabolized by multiple cytochrome P450 (CYP) enzymes and non-CYP enzymes/proteins. At clinically relevant concentrations of MLN2238, in vitro studies using human cDNA-expressed CYP isozymes showed that no specific CYP isozyme predominantly contributes to MLN2238 clearance. At concentrations exceeding those observed clinically (10 µM), MLN2238 was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (< 1%). In contrast, at 0.1 µM and 0.5 µM substrate concentrations, which are closer to clinical concentrations of MLN2238 following oral administration of 4 mg MLN2238, non-CYP–mediated clearance was observed and seemed to play a major role in MLN2238 clearance in vitro. These data indicate that at clinically relevant concentrations of MLN2238, minimal CYP-mediated drug-drug interactions (DDIs) with selective CYP inhibitors would be expected. In addition, MLN2238 is neither a reversible nor a time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.

In a recently concluded, phase 1 DDI study, the PK of MLN2238 (maximum [peak] concentration [C_{max}] and area under the plasma concentration versus time curve [AUC]) was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor (Study C16009, Arm 5) [16]; hence, no dose adjustment is necessary when MLN2238 is administered with strong CYP3A inhibitors. These findings are explained by the in vitro metabolism data indicating the lack of a discernible contribution of CYP-mediated metabolism at clinically relevant MLN2238 concentrations. As discussed earlier, no CYP isoforms have been identified to contribute meaningfully to MLN2238 metabolism at clinically relevant concentrations, and CYP3A contribution to total metabolism was highest across all CYP isoforms when characterized at a supratherapeutic concentration of 10 µM. Therefore, on the basis of the totality of information from the clinical clarithromycin DDI study and the in vitro CYP phenotyping data, it can be concluded that MLN2238 PK is not likely to be altered upon co-administration with any CYP isoform-selective inhibitor, including strong CYP1A2 inhibitors. Consistently in the population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect MLN2238 clearance; therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. MLN2238 may be a weak affinity substrate of P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP) or multidrug resistance associated protein (MRP2) efflux pump transporters. MLN2238 is not an inhibitor of P-gp, BCRP, or MRP2. The potential for

DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

In a recently completed DDI study, co-administration of MLN2238 with rifampin decreased MLN2238 C_{max} by 54% and AUC by 74% (Study C16009, Arm 4). Accordingly, concomitant administration of MLN2238 with strong CYP3A inducers should be avoided.

Additional details on the PK and drug metabolism of MLN9708 are provided in the IB.

1.5 Study Rationale

The recommended course of treatment for patients with newly diagnosed multiple myeloma (NDMM) depends largely on their age and overall health, and thus their ability to tolerate toxic combination therapies. For patients under the age of 65 who are in otherwise good health, the standard treatment for NDMM is high-dose therapy followed by autologous stem-cell transplantation (HDT-ASCT) with or without maintenance.[17,18] On the other hand, HDT-ASCT is not a preferred treatment option for most elderly patients. Randomized trials that demonstrated the superiority of standard dose versus HDT-ASCT were done in patients 65 or younger. Moreover, elderly patients are often not able to tolerate the accompanying toxicity. Because of this, improvements in survival seen over the past decade in patients with MM have been more pronounced in younger patients than in elderly patients.[19] It is hypothesized that the apparent lack in survival progress in these elderly patients may be a result of treatment-related toxicity burden and/or the inability to deliver efficacious therapy.[19] Furthermore, within the heterogeneous elderly patient population, there is a subset of patients who are particularly frail and are especially challenging to treat.[18] The median age of diagnosis for patients with multiple myeloma is between 63 and 70 years, categorizing many newly diagnosed patients as elderly and thus not candidates for transplant.[17] This fact, coupled with lagging survival improvements in the elderly, highlights the clear medical need to develop novel combination therapies with improved efficacy and toxicity profiles. In elderly patients, current treatment options include melphalan-containing regimens (declining in use in recent years due to the known risk of leukemia and myelodysplastic syndrome with melphalan), or a non-melphalan containing regimen such as lenalidomide (an immunomodulatory agent) plus dexamethasone.

Individually and in combination, the proteasome inhibitors and immunomodulatory analogues (IMiDs) have changed the conventional treatment of NDMM. The combination of a proteasome inhibitor, IMiD, and dexamethasone have shown significant improvements largely in terms of overall response rates and are now recognized by the National

Comprehensive Cancer Network (NCCN) as induction therapy for both transplant and nontransplant eligible patients.[20] Studies of SCT, a standard of care for select patients, were conducted before the availability of bortezomib and the IMiDs. More recently, the high response rates reported with these agents in transplant-eligible and -ineligible patients and the reports of similar outcomes when such agents are continued after the induction period and transplant delayed until disease progression–compared to the usual upfront transplant–have raised the questions of the utility of early ASCT and of maintenance therapy in NDMM.[20-22]

Moreover, despite the current therapeutic options, the disease is characterized by frequent relapses and there remains a need for more active, safer, and convenient agents as well as the challenge of combining currently established agents with contemporary novel ones in an attempt to achieve long-term disease control.[23] To examine the feasibility of those objectives, this study is proposed based on the results of bortezomib, Millennium's first generation proteasome inhibitor, and MLN9708, a next generation proteasome inhibitor, will be administered in combination with lenalidomide and dexamethasone. Further support for MLN9708 in this trial is provided by Chauhan and colleagues. Based on their work in in vitro model systems, this group reports MLN2238 combined with lenalidomide or dexamethasone triggers synergistic anti–multiple myeloma activity supporting further clinical evaluation of MLN9708 in combination with these agents.[24]

The purpose of this study is to evaluate whether the addition of MLN9708 to lenalidomide and dexamethasone increases efficacy and safety outcomes in patients with NDMM who are transplant ineligible.

1.6 Rationale for the Combination of MLN9708, Lenalidomide, and Dexamethasone

1.6.1 Combination of MLN9708, Lenalidomide, and Dexamethasone

Standard front-line treatment for patients with multiple myeloma consists of either high-dose induction antineoplastic therapy (HDT) followed by stem cell transplantation (SCT) or antineoplastic therapy alone for those who are not eligible for HDT-SCT.[20,25-28] Oral combination of melphalan and prednisone (MP) and MP-based therapies (VELCADE [bortezomib] +MP; Thalidomide +MP) have been the standard of treatment recommended by the NCCN and European Society for Medical Oncology and for patients with NDMM who are not eligible for HDT-SCT.[17,29,30] The VISTA phase 3 study confirms that the addition of VELCADE to MP was more active than MP-alone and produced a higher health-

related quality of life in this population.[31,32] The NCCN guidelines on Multiple Myeloma and the National Cancer Institute summary of Plasma Cell Neoplasms for Health Professionals recommend combination treatment with a proteasome inhibitor and/or lenalidomide plus dexamethasone for the initial treatment of NDMM in patients who are not candidates for stem cell transplant. Clinical data from multiple studies support the combination of a proteasome inhibitor, an IMiD, and a glucocorticosteroid. The combination of bortezomib, lenalidomide, and low-dose dexamethasone, as noted in Section 1.5 and the NCCN guidelines, illustrates that this combination is very active and well tolerated in the NDMM population.[20,33-35] On the other hand, there is also a solid rationale for the control arm of lenalidomide-dexamethasone (plus placebo), which has demonstrated activity in phase 3 testing in this population.[36,37] Given that MLN9708 has improved binding kinetics and pharmacologic profile compared with bortezomib, it is expected that these differences will translate into similar, if not improved, efficacy and safety profiles.[38] Preclinical work by Chauhan and colleagues also supports clinical evaluation of MLN9708 in combination with lenalidomide and dexamethasone based on their results reporting that MLN2238 combined with lenalidomide or dexamethasone triggers synergistic anti–multiple myeloma activity.[24] Though no clinical studies have been completed with the combination of MLN9708, lenalidomide, and dexamethasone (Study C16005 and Study C16010 are ongoing), the data available with bortezomib forms the foundation for adding the proteasome inhibitor in the combination in this study.

In terms of safety, the toxicological profile of MLN2238 in nonclinical studies is generally consistent with class-based effects of proteasome inhibition and is similar to what has been reported previously in nonclinical studies with bortezomib. The most common treatment-emergent adverse events (TEAE) of single-agent MLN9708 across all dose level cohorts regardless of causality in all phase 1 studies reported to date, as discussed in Section 1.3, were anticipated based on preclinical data and previous experience with bortezomib. Given the available clinical data in Study C16005, the similar nonclinical toxicity profile between MLN2238 and bortezomib, the toxicities demonstrated in studies with lenalidomide and dexamethasone, and the low potential for DDI, it is anticipated that any potential for overlapping toxicities with a combination of MLN9708, lenalidomide, and dexamethasone can be monitored in the clinic with routine clinical observations and clinical pathology assessments.

1.6.2 Rationale for MLN9708, Lenalidomide, and Dexamethasone Dose and Schedule Selection

Oral MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle is supported by nonclinical data and clinical trial results in which MLN9708 has been given as a single agent and in combination with lenalidomide and dexamethasone. The weekly schedule was well tolerated in in vivo toxicology studies and was predicted to allow dosing on a schedule that produced maximum antitumor activity in mouse models. These doses are chosen based on the Study C16005, which is an open-label, dose escalation, phase 1/2 study of MLN9708 dosing on a weekly schedule (Days 1, 8, and 15 of a 28-day cycle) in combination with lenalidomide and low-dose dexamethasone (LenDex) in adult patients with NDMM. In the phase 1 portion of Study C16005, 3 evaluable patients were enrolled in each of the following cohorts: Cohort 1 (1.68 mg/m^2), Cohort 2 (2.23 mg/m^2), Cohort 3 (2.97 mg/m^2), and Cohort 4 (3.95 mg/m^2). While 2.97 mg/m^2 was determined to be the maximum tolerated dose (MTD), 3 out of 6 patients were not able to receive all of their lenalidomide doses during Cycle 1 due to Grade 2 or 3 rash. Given that the dose of MLN9708 at 2.97 mg/m^2 significantly compromised the doses of the LenDex background regimen, and that the dose of 2.23mg/m^2 is very tolerable and clinically active, the sponsor has decided to use 2.23 mg/m^2 as the dose for the phase 2 portion of the C16005 study. Enrollment in Study C16005 has been completed with a total of 65 patients (15 in phase 1 and 50 in phase 2). Final study results are not available, but preliminary data suggests oral MLN9708 given weekly plus lenalidomide and dexamethasone in a 28-day cycle appears well tolerated with manageable toxicity and encouraging antitumor activity. Encouraging signs of antitumor activity were observed with preliminary overall response rates (≥ partial response [PR]) of 91% and a complete response (CR) + very good partial response (VGPR) rate of 39% in a setting where patients have received a median of 4 cycles of therapy (range 1-15) as of the 30 April 2012 data cut. In the MTD cohorts, fatigue was the most common adverse event (AE) reported (38%). Other common AEs (at least 15%) reported include nausea (32%); constipation (30%); upper respiratory infection (23%); peripheral edema (21%); thrombocytopenia, vomiting, and diarrhea (19% each); anemia, fever, and back pain (17% each); and dysgeusia (15%). Skin toxicity, primarily erythematous rash, occurred in 62% of patients (of note, rash is an overlapping toxicity with MLN9708 and lenalidomide). Peripheral neuropathy was reported in 13% of patients; Grade 3 in 1 patient. The data today support further clinical study of MLN9708 in combination with LenDex in patients with NDMM.

This recommended starting dose of 2.23 mg/m^2 is translated into a fixed dose of 4.0 mg based on the results from population PK analysis. A population PK model was built using data from both the TW and W IV (N = 86) and oral (N = 51) dosing regimens (N = 137). Population PK analysis showed that MLN9708 PK can be well described by a 3-compartment model with linear elimination for IV data and with an additional absorption compartment (first order absorption) for oral administration (PO) data. Covariate analyses indicate that interpatient variability in BSA and/or body weight did not significantly contribute to the variability in CL and volume of distribution in the central compartment (V2). CL and V2 are the PK parameters that will affect AUC and C_{max}. The lack of a discernable relationship between BSA and MLN9708 CL based on data in 137 patients over a relatively wide BSA range (1.4-2.6 m^2) indicates that total systemic exposure (AUC) following fixed dosing should be independent of the individual patient's BSA (see Figure 1-1). Accordingly, the starting dose of MLN9708 in the phase 2 portion of Study C16005 is a fixed dose of 4.0 mg, based on the recommended dose of 2.23 mg/m^2 (using mean patient BSA of 1.86 m^2 from the 2208 MM patients in bortezomib clinical trials for conversion to fixed dose).

Figure 1-1 No Apparent Relationship Between MLN9708 Clearance and BSA

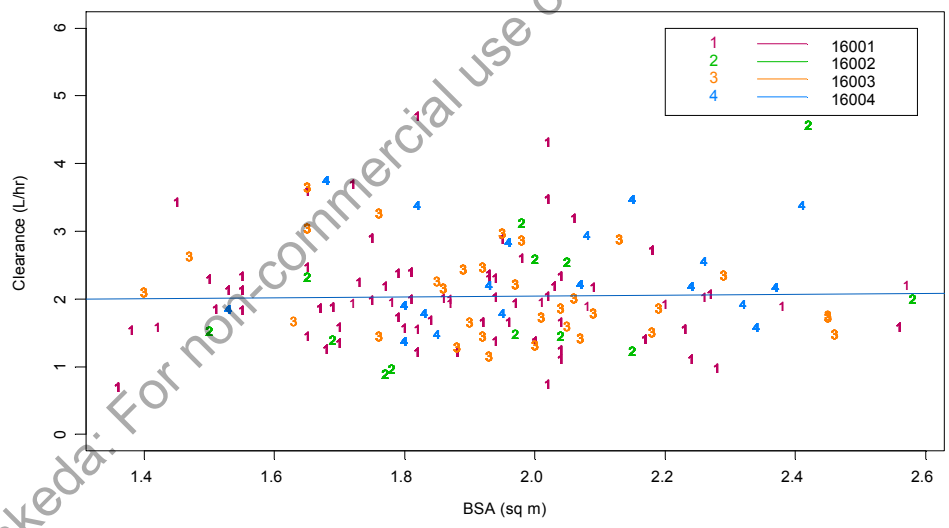

Figure 1-1 provides a plot of individual values of MLN9708 clearance across the range of BSA (1.4-2.6 m^2) from 4 phase 1 studies (N = 137). Each color identifies each study, and the blue line represents linear regression line.

CCI

[redacted]

CCI [redacted] genes will be also assessed as they may relate to CCI [redacted] in the tumor or in the host microenvironment, impacting the growth, survival, and/or drug resistance of a given patient's myeloma. Additional associations with either the efficacy or safety of MLN9708 may be examined if there is a reasonable approach to identify myeloma patient populations with differential risk to benefit ratios upon treatment with MLN9708.[44,45]

CCI [redacted]

1.6.4 Rationale for the Combination of MLN9708, Lenalidomide, and Dexamethasone in Patients with High-Risk Cytogenetic Characteristics

The clinical outcome of multiple myeloma patients is highly variable and can be related to specific cytogenetic subtypes. Abnormalities such as t(11;14), t(6;14), and hyperdiploidy are associated with neutral or favorable prognosis while t(4;14), t(14;16), deletion of 17p, and amplification of 1q21 impart an unfavorable prognosis.[50] Some reports suggest that bortezomib treatment, in combination with lenalidomide, is able to overcome the adverse effects associated with high-risk cytogenetics, whereas other studies show contradicting results. Recently Dimopoulos et al., has described the outcome of these subtypes in the context of patients with relapsed and refractory MM treated with lenalidomide and dexamethasone (RD) with or without bortezomib.[51] In this study poor risk cytogenetic populations were associated with lower response rate, which was significant in the RD arm ($p = 0.01$), but not in the RD with bortezomib (VRD) arm ($p = 0.219$). The adverse effect of del13q, amp(1q21), and t(4;14) were more pronounced mainly for the RD-treated patients. Despite the responses observed in the high-risk cytogenetics groups with VRD, the PFS and

OS in these patients, especially the del(17p) group, was significantly worse than standard risk patients ($p < 0.001$ and $p = 0.017$ respectively). One potential reason the VRD responses in del(17p) did not translate into improved time to event could be the difference in length of treatment between RD and VRD arms. Patients enrolled in the RD arm were treated until progression or until unacceptable toxicity arise. Differently, patients enrolled in the VRD arm received the treatment for only 8 cycles, then VELCADE was dropped, and patients who did not progress at that time were treated with RD until progression.

The aggressive del(17p) myelomas may require long-term treatment with a proteasome inhibitor. This hypothesis is further supported by Neben at al., where it was shown that VELCADE based treatment before and after ASCT in NDMM improves outcome in patients with del(17p) compared to control therapy.[52] In this phase 3 study, the bortezomib, adriamycin, and dexamethasone regimen was compared to vincristine, adriamycin, and dexamethasone. PFS and OS were compared in the whole population and specifically in the high-risk cytogenetic populations. Median PFS and OS (3 years) rates were at least comparable or superior in the bortezomib-containing arm compared to the standard arm. However, a statistical significant difference was found only for patients carrying the del(17p) abnormality. PFS in del(17p)-positive patients was 26.2 months in the bortezomib containing arm, compared to 12 months in the standard arm. Similarly, 3-year OS benefit in patients with del(17p) was 69% in the bortezomib-containing regimen vs 17% in the standard arm, while it was 80% in the bortezomib arm versus 85% in the standard arm in patients without del(17p).

1.6.5 Minimal Residual Disease Assessment

Complete response remains the optimal objective in front-line treatment of myeloma to improve survival. The definition of CR has evolved in recent years from normalization of serum protein electrophoresis and bone marrow morphology with negative immunofixation to normal serum free light-chain ratio test (stringent CR), and more recently to normal immunophenotypic response (IR). Immunophenotyping defines a tumor's surface marker profile via flow cytometry and is highly sensitive to the presence of tumor cells in marrow specimens. Patients with tumor cells below the detection threshold (1 MM cell in ~ 10,000 cells) are considered to be in a flow cytometric remission. Although the long-term utility of this approach is still in its early day in MM, several studies have indicated that MRD -negative patients experienced longer PFS and OS than flow cytometric-positive patients. Recently, Paiva and colleagues from Salamanca, Spain, have investigated the impact of IR versus CR and stringent CR in 260 newly diagnosed elderly (> 65 years)

patients with multiple myeloma treated with novel agents in the PETHEMA/GEM 05 trial.[53] In this trial, IR showed significantly increased 3-year rates of PFS and TTP as compared with those in stringent CR or CR (90% vs 69% and 60%, and 96% vs 71% and 68% [$p < 0.001$], respectively). On a multivariate COX regression analysis for PFS, only IR status was an independent prognostic factor (relative risk, 4.1; 95% confidence interval [CI], 1.4-12.0; $p < 0.01$).

In this study, the assessment of MRD will be done using bone marrow aspirates collected when a patient is suspected to have reached CR at any time during the conduct of the entire study. A repeat bone marrow aspirate will be obtained at Cycle 18 for only those patients who have maintained a CR until that point. This repeat bone marrow aspirate may be collected up to 4 weeks after Cycle 18, Day 1 to assess MRD.

If a patient has had MRD testing because of a suspected CR within 2 cycles of Cycle 18, then this repeat MRD assessment does not need to be performed. Samples are required to be sent to a central lab for analysis. These samples will be processed according to the Laboratory Manual.

1.6.6 Rationale for Bone Disease Assessment

Bone disease is a common feature of MM, occurring in more than 80% of patients, and can result in bone pain, fractures, spinal cord compression, and hypercalcemia. There is increasing evidence that bortezomib has a positive effect on bone metabolism, and MLN9708 may have a similar positive effect. Bortezomib therapy has been associated with a reduction in bone disease-related myeloma progression events, increases in bone density, and favorable changes in bone biomarkers.[54] The phase 3 VISTA trial randomized 682 patients with NDMM to melphalan/prednisone with or without the addition of bortezomib. The bortezomib group had lower rates of disease progression due to worsening bone disease (3% vs 11%), lower rates of bisphosphonate use (73% vs 82%), and a lower requirement for subsequent radiotherapy (3% vs 8%).[55]

This study will build on the VISTA trial by studying skeletal-related events (SRE), bone density, CCI [redacted] using blood samples.

1.6.7 Rationale for Selected Subgroups

If the test for PFS in the intent-to-treat (ITT) population is not statistically significant at the first interim analysis (IA), PFS will be tested at IA2 in both the ITT population and in

3 prespecified subgroups: 1) patients with baseline creatinine clearance (CrCl) > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21). These subgroups were selected on the basis of recent data suggesting the potential for treatment benefit in these patients:

- Worse outcomes following treatment with continuous lenalidomide/dexamethasone have been observed in patients with CrCl ≤ 60 mL/min and patients aged ≥ 75 years [56-59]. Therefore, it could be clinically plausible that in a renally impaired (CrCl ≤ 60 mL/min) or older (≥ 75 years) subpopulation, the already higher risk/benefit ratio (less tolerability with less efficacy) is further affected by the addition of a third agent.

- In addition, the International Myeloma Working Group consensus has recently identified cytogenetic abnormalities as conferring poor prognosis [60,61]. However, patients harboring high-risk cytogenetic abnormalities may derive particular benefit in this trial on the basis of data showing improved treatment outcomes in patients with relapsed and/or refractory multiple myeloma treated with ixazomib (MLN9708) in combination with lenalidomide/dexamethasone in Study C16010 and in patients with newly diagnosed multiple myeloma treated with another proteasome inhibitor (bortezomib) [62-65].

1.7 Potential Risks and Benefits

As of the clinical cutoff date of 30 April 2012, 382 patients across 9 ongoing sponsor-led studies have been treated with MLN9708. Clinical safety data includes experience from patients who received multiple cycles followed by treatment-free periods and from patients who reduced or discontinued treatment. The emerging safety profile indicates that the AEs reported with MLN9708 are consistent with the known effects of proteasome inhibition and are similar to what has been previously reported with VELCADE, though the frequency and severity may slightly differ. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention. It is possible that MLN9708 will have toxicities that were not predicted from its evaluation in nonclinical studies or previously observed in ongoing clinical studies. To mitigate the inherent risks in clinical studies of MLN9708, patients are monitored closely for anticipated toxicities. Guidance for the management of AEs and procedures for reducing doses are provided in the protocols, and drug dosage can be reduced by either reducing the dose administered or by interruption of the scheduled treatment within a cycle.

MLN9708 shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. To date, antitumor activity has been seen with single-agent MLN9708, when combined with established therapies, and across all malignancies studied (advanced solid tumors, non-Hodgkin lymphoma, RRMM, relapsed and/or refractory systemic light chain amyloidosis [RRAL], and newly diagnosed multiple myeloma [NDMM]). Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of MLN9708.

Further information can be found in the MLN9708 IB.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is:

- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves PFS in patients with NDMM

2.2 Secondary Objectives

The key secondary objectives are:

- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves OS
- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves the rate of CR
- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves pain response rate, as assessed by the Brief Pain Inventory-Short Form (BPI-SF) and analgesic use

Other secondary objectives include:

- To determine overall response rate (ORR), including PR, VGPR, and CR
- To determine time to response (TTR), DOR, and TTP

- To determine the effect of the addition of MLN9708 to lenalidomide and dexamethasone on progression-free survival 2 (PFS2), defined as the date from randomization to the date of second disease progression or death from any cause, whichever comes first

- To determine the safety of the addition of MLN9708 to lenalidomide and dexamethasone

- To assess change in global health status, as measured by the global health status, functioning, and symptoms as measured by the patient-reported outcome (PRO) instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and MY-20 module

- To determine the PFS and OS in high-risk cytogenetic patient groups defined by the following cytogenetic abnormalities: t(4;14), t(14;16), amp(1q21), and del(17p)

- To evaluate minimal residual disease status (MRD), via flow cytometry, in patients suspected to have reached CR at any time during the entire conduct of the study, and at Cycle 18 for patients who have maintained a CR until that point. The impact of MRD status on TTP, PFS, and OS will be assessed.

- To assess time to pain progression

- To collect PK data to contribute to population PK analyses

- To evaluate the frequency of SREs (eg, new fractures [including vertebral compression fractures], irradiation of or surgery on bone, or spinal cord compression) from baseline through the last survival assessment

2.3 Exploratory Objectives

CCI

[redacted]

CCI

[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is:

- PFS, defined as the time from the date of randomization to the date of first documentation of disease progression based on central laboratory results and international myeloma working group (IMWG) criteria as evaluated by an independent review committee (IRC), or death due to any cause, whichever occurs first

3.2 Secondary Endpoints

The key secondary endpoints are:

- OS, measured as the time from the date of randomization to the date of death
- CR rate
- Pain response rate, measured by the proportion of pain responders, as determined by the BPI-SF and analgesic use

Other secondary endpoints are:

- Overall response rate (CR + VGPR + PR)
- Time to response, measured as the time from randomization to the date of first documented objective response
- Duration of response, measured as the time from the date of first documentation of response to the date of first documented progression
- Time to progression, measured as the time from randomization to the date of first documented progression
- PFS2, defined as the time from the date of randomization to the date of second documentation of disease progression (on subsequent line of anticancer therapy), as assessed by the investigator in accordance with IMWG criteria, or death due to any cause, whichever comes first
- Eastern Cooperative Oncology Group (ECOG) performance scores, AEs, serious adverse events (SAEs), and assessments of clinical laboratory values
- Comparison of change in global health status between baseline and each postbaseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30 and MY-20
- OS and PFS in high-risk population carrying del(17p), amp(1q21), t(4;14), or t(14;16)

- Estimate the frequency of detection of MRD via flow cytometry in patients assessed at suspected CR at any time during the entire conduct of the study and in patients who have maintained CR until Cycle 18, and its impact on TTP, PFS, and OS
- Time to pain progression, as assessed by the time from randomization to the date of initial progression classification
- Plasma concentration-time data to contribute to future population PK analysis
- Development of new or worsening of existing SREs, defined as new fractures (including vertebral compression fractures), irradiation of or surgery on bone, or spinal cord compression

3.3 Exploratory Endpoints

CCI

CCI

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This is a phase 3, randomized, double-blind, multicenter study in patients with NDMM to evaluate the safety and efficacy of oral MLN9708 versus placebo when added to lenalidomide and dexamethasone. Adult patients with a confirmed diagnosis of symptomatic MM who have not received previous antimyeloma treatment, who are ineligible for high-dose therapy plus stem cell transplantation (HDT-SCT) because of age (ie, ≥ 65 years) or coexisting conditions per investigator judgment, who are candidates for treatment with LenDex as their standard therapy, and who meet all other eligibility criteria (see Section 5) will be enrolled in this study. Approximately 701 patients will be enrolled in the study.

General eligibility criteria may be assessed prior to the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events, formal screening will occur during the Screening period, which may last for up to 28 days prior to randomization. A Millennium Pharmaceuticals, Inc. (MPI)/designee clinician will confirm patient eligibility prior to randomization by the investigator.

Following the Screening period, patients to be enrolled will be randomized to receive MLN9708 or placebo in a double-blind fashion, in addition to the background therapy of LenDex. Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms, stratified by age (< 75 years vs ≥ 75), International Staging System (ISS) (stage 1 or 2 vs stage 3), and BPI-SF worst pain score (< 4 vs ≥ 4) at screening.

Patients will receive study drug (MLN9708 4.0 mg or matching placebo capsule) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients over 75 years of age at randomization will receive reduced dexamethasone dose (20 mg). Patients with a low creatinine clearance of

≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) but ≥ 30 mL/min will receive a reduced lenalidomide dose of 10 mg once daily (QD) on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg QD after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg QD. Dose modifications may be made throughout the study based on toxicities.

Patients may continue to receive treatment as detailed previously for 18 cycles, or until progressive disease (PD) or unacceptable toxicity, whichever comes first. After 18 cycles, patients remaining on treatment will continue the study drug regimen in the same randomization arm on the same schedule with modified dose levels of study drug and lenalidomide until disease progression or unacceptable toxicity (see Table 4-1). Dose modifications should be made based on prior dose modifications during the first 18 cycles of treatment.

Table 4-1 Dose Level Changes Beyond 18 Cycles of Treatment

Drug	Dose (≤ 18 Cycles)	Dose (> 18 Cycles)
MLN9708/Placebo	4.0 mg	3.0 mg
	3.0 mg[a]	3.0 mg
	2.3 mg[a]	2.3 mg
Lenalidomide	25 mg[b]	10 mg
	15 mg[a]	10 mg
	10 mg[a]	10 mg
	5 mg[a]	5 mg
Dexamethasone	40 mg[c]	none

a Dose reduction within first 18 cycles of treatment due to toxicity.

b Patients with a low creatinine clearance of ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) but ≥ 30 mL/min will receive a reduced lenalidomide dose of 10 mg QD on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg QD after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg QD.

c Patients over 75 years of age at randomization will receive a reduced dexamethasone dose (20 mg).

The treatment period of the study is defined as any time a patient is receiving any of the study drug regimen, and will be comprised of 28-day treatment cycles. Patients will be seen at regular treatment cycle intervals while they are participating in the study: weekly for the

first 2 cycles, twice a treatment cycle during the third cycle, and then once a treatment cycle for the remainder of their participation in the treatment period, until they experience disease progression or discontinue for alternate reasons. Patients will then enter either the PFS follow-up period (for patients who discontinue before disease progression) or the OS follow-up period (for patients who have disease progression during the treatment period).

Patients will be assessed for disease response and progression by the investigator and an IRC. Response will be assessed according to the IMWG uniform response criteria (Section 15.11) for all patients every cycle during the treatment period. For patients who discontinue treatment before disease progression, response will also be assessed in accordance with the IMWG uniform response criteria every 4 weeks during the PFS follow-up period until disease progression is confirmed or the patients are started on another anticancer therapy; radiographic disease assessments are to be performed every 8 weeks for patients with documented extramedullary disease. Following disease progression or start of another anticancer therapy, patients will enter the OS follow-up period and will be contacted every 12 weeks until death or termination of the study by the sponsor. All subsequent anticancer therapies for MM will be reported as part of the OS follow-up period assessments. In addition, patients who receive a subsequent anticancer therapy for MM will be assessed by the investigator (according to the IMWG uniform response criteria [Section 15.11]) for disease response (at minimum, disease progression) to determine PFS2 on the next line of therapy. Response assessments should be made using local laboratory results, and the frequency will be determined by the investigator (recommended every 12 weeks). Results will be recorded in the electronic case report form (eCRF) every 12 weeks until PFS2 is reported or a new (third) line of anticancer therapy is started, whichever comes first.

Pain evaluation (using the BPI-SF) will include quantified assessments of intensity, frequency and duration, degree of discomfort, location, and likely relationship to MM (versus comorbidities). Time to pain progression will be based on pain assessments using the worst pain item on the BPI-SF rated on a scale from 0 to 10, collected as outlined in the Schedule of Events. Health-related quality of life (QOL) will also be evaluated through patient self-reported instruments including the EORTC QLQ-C30, MY-20, and the EQ-5D generic health status measure. In addition to assessing selected symptoms, these instruments elucidate the effects of disease on physical, social, psychological/emotional, and cognitive functioning.

ECOG performance score and AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of MLN9708. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010.

Unscheduled visits may occur between treatment cycles as required. For example, symptomatic pain progression should result in an interim unscheduled visit, as would ongoing Grade 3 or worse AEs.

Patients will attend an EOT visit 30 days (+1 week) after receiving their last dose of the study drug regimen unless next-line therapy is started before 30 days after the last dose of study drug, in which case the EOT visit should occur before the start of the next-line therapy. Patients will continue to be followed for other follow-up assessments specified in the Schedule of Events.

Two IAs are planned to occur during the study. The first analysis will be performed when approximately 326 PFS events (disease progression or death) have occurred. If the test for PFS in the ITT population is statistically significant at the first IA, this will be the final analysis (FA) for PFS for statistical testing purposes; central efficacy and investigator assessments for protocol purposes will be stopped and not recorded in the eCRF except for investigator assessment of PFS2 (see Schedule of Events). In such a case, the second IA will assess OS when approximately 250 death events have occurred. If the test for PFS in the ITT is not statistically significant at the first IA, then central efficacy and investigator response assessments will continue until the second IA, which will assess PFS and OS.

Upon implementation of this amendment (Protocol Amendment 4), the second IA will be conducted when approximately 370 PFS events have occurred (rather than the previous study design of 435 PFS events). In addition, PFS will be tested at IA2 in both the ITT population and in 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21).

The final OS analysis will be performed when approximately 320 to 400 deaths have occurred with the total event size calculation based on the adaptive sample size re-assessment approach.[66,67] The trial will be stopped for overwhelming efficacy if the O'Brien-Fleming efficacy boundary of OS is crossed.

An independent data monitoring committee (IDMC) will review safety and efficacy data at the IAs. See Section 9.2 for more information.

4.2 Number of Patients

Approximately 701 patients will be enrolled in this study from approximately 150 study centers in North America, Europe, Russia, New Zealand, and Asia. Enrollment is defined as being randomized to treatment in the study.

4.3 Duration of Study

It is anticipated that this study will last for approximately 87 months, including a 27-month randomization period and an additional 60-month (5-year) follow-up from the last patient enrolled.

5. STUDY POPULATION

Adult patients age 18 or older with a confirmed diagnosis of symptomatic MM who have received no prior antimyeloma treatment and who are ineligible for HDT-SCT due to age (≥ 65 years) or comorbidities will be enrolled in this study.

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be randomized to treatment:

1. Adult male or female patients 18 years old and above with a confirmed diagnosis of symptomatic multiple myeloma according to IMWG criteria (see Section 15.2) who have not received prior treatment for multiple myeloma

2. Patients for whom lenalidomide and dexamethasone treatment is appropriate and who are not eligible for HDT-SCT for 1 or more of the following reasons:

    - The patient is 65 years of age or older

    - The patient is less than 65 years of age but has significant comorbid condition(s) that are, in the opinion of the investigator, likely to have a negative impact on tolerability of HDT-SCT

3. Patients must have measurable disease defined by at least 1 of the following 3 measurements:

   - Serum M-protein ≥ 1 g/dL (≥ 10 g/L)
   - Urine M-protein ≥ 200 mg/24 hours
   - Serum free light chain assay: involved free light chain level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum free light chain ratio is abnormal

4. Patients must meet the following clinical laboratory criteria:

   - Absolute neutrophil count (ANC) ≥ 1,000/mm^3 and platelet count ≥ 75,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to randomization
   - Total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN.
   - Calculated creatinine clearance ≥ 30 mL/min, as calculated using the Cockcroft-Gault Equation (Section 15.3).

     NOTE: Patients with a low creatinine clearance ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) but ≥ 30 mL/min will receive a reduced lenalidomide dose of 10 mg QD on Days 1 through 21 of a 28-day cycle; patients with a creatinine clearance < 30 mL/min are not permitted to be enrolled into the study. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg QD.

5. ECOG performance status of 0, 1, or 2.

6. Female patients who:

   - Are postmenopausal for at least 24 months before the Screening visit, OR

- Are surgically sterile, OR

- Females of childbearing potential ([FCBP] – see Section 6.9 for definition) must:

  a. All countries except Canada: Have TWO medically-supervised negative pregnancy tests (serum or urine with sensitivity of at least 25 mIU/mL), even if continuous abstinence is the chosen method of contraception. One test must be obtained within 10 to 14 days and the other test must be obtained within 24 hours prior to administering the first dose of the study drug regimen at Cycle 1, Day 1. The dates and results of pregnancy tests must be documented

  b. Canada: Have TWO medically supervised negative serum pregnancy tests with a sensitivity of at least 25 mIU/mL prior to the first dose of the study drug regimen, even if continuous abstinence is the chosen method of contraception. One test must be obtained within 7 to 14 days and the second within 24 hours prior to administering the first dose of the study drug regimen at Cycle 1, Day 1. The dates and results of pregnancy tests must be documented

  c. Either agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception) OR begin TWO reliable methods of birth control: 1 highly effective method and 1 additional effective method AT THE SAME TIME (refer to Section 6.9), at least 28 days before starting the study drug regimen through 90 days after the last dose of study treatment

  d. Agree to ongoing pregnancy testing

  e. Adhere to the guidelines of the Revlimid REMS™ (formerly known as RevAssist®) program (United States [US] participants), RevAid® program (Canadian participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial Revlimid supplies). The counseling must be documented.

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

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception) OR

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy, AND

- Adhere to the guidelines of the Revlimid REMS™ (formerly known as RevAssist®) program (US participants), RevAid® program (Canadian participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial Revlimid supplies). The counseling must be documented.

7. Suitable venous access for the study-required blood sampling

8. Must be able to take concurrent aspirin 70 to 325 mg daily (or equivalent dose per country product label [package insert (PI) or Summary of Product Characteristics (SmPC)]) or enoxaparin 40 mg subcutaneously daily (or its equivalent) if allergic to aspirin, per published standard or institutional standard of care, as prophylactic anticoagulation prior to randomization.
   NOTE: For patients with prior history of deep vein thrombosis (DVT), low molecular weight heparin (LMWH) is mandatory. (See Section 6.10 for thromboembolism prophylaxis.)

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

10. Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be randomized to treatment:

1. Prior treatment for multiple myeloma with either standard of care treatment or investigational regimen
   NOTE: Prior treatment with corticosteroids or localized radiotherapy is permitted as long as it is below a therapeutic level (maximum dose of corticosteroids should not exceed the equivalent of 160 mg of dexamethasone over a 2-week period [see Table 15-3])

2. Localized radiotherapy within 14 days before randomization

3. Diagnosed and treated for another malignancy within 5 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease
   Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone histologically confirmed complete surgical resection

4. Inability or unwillingness to receive thromboembolism prophylaxis

5. Female patients who are lactating and breastfeeding or have a positive pregnancy test during the Screening period

6. Major surgery within 14 days before randomization.
   NOTE: Kyphoplasty or vertebroplasty is not considered major surgery

7. Central nervous system involvement

8. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before randomization

9. Diagnosis of Waldenstrom's macroglobulinemia, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome

10. Evidence of current uncontrolled cardiovascular conditions within 6 months prior to randomization, including:

    - Uncontrolled hypertension, cardiac arrhythmias, or congestive heart failure
    - Unstable angina, or
    - Myocardial infarction

11. Systemic treatment 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 within 14 days before randomization in the study

12. Ongoing or active infection, or active hepatitis B or C infection, or known human immunodeficiency virus positive

13. Comorbid systemic illnesses or other severe concurrent disease which, 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 (eg, peripheral neuropathy that is Grade 1 with pain or Grade 2 or higher of any cause)

14. Psychiatric illness/social situation that would limit compliance with study requirements

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

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

17. Treatment with any investigational products within 60 days before randomization

6. STUDY DRUG

All protocol eligibility criteria must be met before randomization and documented in the eCRF before study drug regimen administration. The study drug regimen will be administered only to randomized patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity as necessary and doses of the appropriate drug should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of dose.

All doses must be taken as outlined in the Schedule of Events. Eligible patients may take the study drug regimen at home as directed. Refer to the Study Manual for additional instructions regarding study drug administration.

6.1 Test Article (MLN9708) and Matched Placebo

MLN9708 capsules and matching placebo capsules will be subsequently referred to as study drug. Study drug in combination with lenalidomide and dexamethasone will be referred to as study drug regimen.

This is a double-blind, placebo-controlled study, and study drug will contain either MLN9708 or placebo. MLN9708 active capsules will be supplied as single capsules at 3 different dose strengths, containing 4.0, 3.0, and 2.3 mg of MLN9708. Placebo capsules will be identical in shape, size, and color to the MLN9708 active capsules. Both the active and placebo capsules will be provided by the sponsor.

During the first 18 cycles of treatment, study drug will be given as a single, oral dose of 4.0 mg weekly (Days 1, 8, and 15) for 3 weeks, followed by 1 week without study drug in a 28-day cycle. After 18 cycles of treatment, if the patient is still receiving the study drug regimen, study drug will be given as a single, oral dose of 3.0 mg weekly on the same schedule as above. If the dose of study drug was reduced to 2.3 mg during the first 18 cycles of treatment, the patient will remain on 2.3 mg after 18 cycles of treatment (see Table 4-1).

Patients should be instructed to swallow 1 capsule of study drug whole with water and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. The capsule should be swallowed with water. A total of approximately 240 mL of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers as long as 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.

6.2 Background Therapies

6.2.1 Lenalidomide Administration

During the first 18 cycles of treatment, lenalidomide will be given as a single, daily, oral dose of 25 mg for a total of 21 days out of a 28-day cycle. Patients with a low creatinine clearance ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) but ≥ 30 mL/min will receive a reduced lenalidomide dose of 10 mg QD on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg QD after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg QD.

After 18 cycles of treatment, if the patient is still receiving the study drug regimen, a reduced lenalidomide oral dose of 10 mg daily will be given as on the same schedule as above. If the dose of lenalidomide was reduced to 5 mg during the first 18 cycles of treatment, the patient will remain on the 5 mg dose after 18 cycles of treatment (see Table 4-1).

Administration of lenalidomide will be at approximately the same time each day, and may be with or without food. Patients should be instructed to swallow lenalidomide capsules whole with water and not to break, chew, or open the capsules.

If a patient misses a dose of lenalidomide, he/she may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take lenalidomide at the usual time. A patient should not take 2 doses of lenalidomide to make up for the one that they missed. 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.

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.

Upon implemention of this amendment, lenalidomide may be administered as commercial REVLIMID or as generic lenalidomide through clinical trial material.

6.2.2 Dexamethasone Administration

During the first 18 cycles of treatment, dexamethasone will be given as a single, oral dose of 40 mg/day weekly on Days 1, 8, 15, and 22 of a 28-day cycle. Patients over 75 years old (at randomization) will receive a reduced dose of dexamethasone (20 mg, same schedule).

After 18 cycles of treatment, if the patient is still receiving the study drug regimen, dexamethasone will be discontinued.

Dexamethasone should be taken at approximately the same time each day. Each dose of dexamethasone should be taken with food or liquid (ie, milk) to avoid stomach irritation, according to the local label/practice.

If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers as long as 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.

6.3 Dose-Modification Guidelines

The patient will be evaluated for possible toxicities that may have occurred after the previous dose(s) according to the Schedule of Events. Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Each adverse event should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Reduction or discontinuation of 1 agent and not the other is appropriate if the toxicity is suspected to be related primarily to 1 of the agents; however, dose reduction of multiple agents is permitted for overlapping toxicities after consultation with the Millennium clinician/study clinician designee. Prior to beginning the next cycle of treatment, refer to the guidelines in Section 6.5.

Further clarification can be obtained in consultation with the Millennium clinician/study clinician designee. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the highest CTCAE toxicity grade.

Alternative dose modifications may be recommended after discussion with the investigator and MPI clinician/designee to maximize exposure of study treatment while protecting patient safety. After initiation of lenalidomide and dexamethasone, dose modification of those drugs should be based on individual patient treatment tolerance, as described in the PI/SmPC.

6.4 Criteria for Dose Modification (Delays, Reductions, and Discontinuations)

Sections 6.4.1 through 6.4.4 detail within cycle dose modifications for toxicity. See Section 6.5 for information on criteria for toxicity recovery before beginning the next cycle of treatment.

6.4.1 Dose Adjustments for Hematologic and Nonhematologic Toxicity: Study Drug and Lenalidomide

A decision regarding dose reduction of study drug and/or lenalidomide will be dependent upon the toxicity, its onset, and time course. Alternative dose modifications may be recommended after discussion with the investigator and Millennium clinician/study clinician designee to maximize exposure of study treatment while protecting patient safety given that there may be overlapping dose-limiting toxicities (eg, thrombocytopenia, neutropenia, rash, and peripheral neuropathy (see Table 6-1, Table 6-2, Table 6-3, and Table 6-5 respectively).

Table 6-1 Study Drug and Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Action on Study Drug (MLN9708/Placebo)	Action on Lenalidomide[68]	Action
First fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow complete blood count (CBC) weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if study drug dose was 4 mg, reduce to 3 mg
Third fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg

Table 6-1 Study Drug and Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Action on Study Drug (MLN9708/Placebo)	Action on Lenalidomide[68]	Action
Fourth fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if study drug dose was 3 mg, reduce to 2.3 mg Discontinue study drug if the 2.3 mg dose is not tolerated
Fifth fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Discontinue lenalidomide if the 5 mg dose is not tolerated

Abbreviations: CBC = complete blood count; mg = milligram; mm^3 = cubic millimeter.
Please refer to Section 6.5 for the required platelet count before initiating the next cycle of treatment.

Table 6-2 Study Drug and Lenalidomide Dose Adjustment for Neutropenia

Absolute Neutrophil Count	Action on Study Drug (MLN9708/Placebo)	Action on Lenalidomide[68]	Action
First fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if study drug dose was 4 mg, reduce to 3 mg
Third fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume and **maintain** dose level lower	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if study drug dose was 3 mg, reduce to 2.3 mg Discontinue study drug if the 2.3 mg dose is not tolerated.
Fifth fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations.
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume and **maintain** dose level lower	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Discontinue lenalidomide if the 5 mg dose is not tolerated.

Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count; G-CSF = granulocyte colony-stimulating factor; L = liter; mg = milligram.
Please refer to Section 6.5 for the required ANC values before initiating the next cycle of treatment.

Table 6-3 Study Drug and Lenalidomide Dose Adjustment for Rash

CTCAE Grade	Action on Study Drug (MLN9708/Placebo)	Action on Lenalidomide[68]	Action[a]
First occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations noted in Section 6.10
Return to < Grade 2 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level[68]	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations, including prophylactic treatment, in Section 6.10
Return to < Grade 2 within the same cycle	For Grade 2, resume and **maintain** dose level For Grade 3, resume study drug at next **lower** dose level	For Grade 2, resume and **maintain** dose level For Grade 3, resume and **maintain** dose level	Eg, if study drug dose was 4 mg, reduce to 3mg
Third occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations, including prophylactic treatment, noted in Section 6.10
Return to < Grade 2 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations, including prophylactic treatment, noted in Section 6.10
Return to < Grade 2 within the same cycle	For Grade 2, resume and **maintain** dose level For Grade 3, resume study drug at next **lower** dose level	For Grade 2, resume and **maintain** dose level For Grade 3, resume and **maintain** dose level	Eg, if study drug dose was 3 mg, reduce to 2.3 mg Discontinue study drug if the 2.3 mg dose is not tolerated
Fifth occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations, including prophylactic treatment, noted in Section 6.10
Return to < Grade 2 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Discontinue lenalidomide if the 5 mg dose is not tolerated

In some severe situations, both lenalidomide and study drug may be interrupted if needed or alternative dose modification management implemented based on discussion between the treating physician and Millennium clinician/study clinician designee. Angioedema and Grade 4 rash have been reported with lenalidomide and should result in lenalidomide discontinuation.[68]

a Please refer to Table 6-7 for additional information on lenalidomide treatment modification for rash.

6.4.2 Study Drug Treatment Modification

Dose adjustments are allowed based on clinical and laboratory findings. Sequential dose reductions of study drug from the starting dose of 4.0 mg daily are recommended for toxicity as indicated in Table 6-4. Treatment modifications due to study drug-related AEs are outlined in Table 6-5.

Table 6-4 Dose Reduction Steps for Study Drug

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
4.0 mg	3.0 mg	2.3 mg	Discontinue study drug

Table 6-5 Study Drug Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events

Adverse Event (Severity)	Action on Study Drug/Placebo	CTC Definitions/ Further Considerations
Peripheral Neuropathy		
Grade 1 peripheral neuropathy	No action	Grade 1 signs & symptoms: asymptomatic, without pain or loss of function, clinical or diagnostic observations only[68]
Grade 1 peripheral neuropathy with pain or Grade 2	Hold study drug until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs & symptoms: moderate symptoms, limiting instrumental activities of daily living (ADL)[68]
Grade 2 peripheral neuropathy with pain or Grade 3	Hold study drug until resolution to Grade ≤ 1 without pain or baseline Reduce study drug to next lower dose upon recovery	Grade 3 signs & symptoms: severe symptoms, limiting self care ADL, assistive device indicated[68]
Grade 4 peripheral neuropathy	Discontinue study drug	

Table 6-5 Study Drug Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events

Adverse Event (Severity)	Action on Study Drug/Placebo	CTC Definitions/ Further Considerations
Nonhematologic Toxicity		
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 6.10
If does not recover 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	Consider permanently discontinuing study drug	Exception, in a case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the MPI/designee clinician

Abbreviations: ADL = activities of daily living; MPI = Millennium Pharmaceuticals, Inc.

6.4.3 Lenalidomide Treatment Modification

Dose adjustments are allowed based on clinical and laboratory findings. Sequential dose reductions from the starting dose of 25 mg daily are recommended for toxicity as indicated in Table 6-6. Treatment modifications due to lenalidomide-related AEs are outlined in Table 6-7. Alternative dose modifications may be recommended after discussion with the investigator and Millennium project clinician/designee to maximize exposure of study treatment while protecting patient safety.

Table 6-6 Dose Reduction Steps for Lenalidomide

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction	Fourth Dose Reduction
25 mg QD	15 mg QD	10 mg QD	5 mg QD	Discontinue lenalidomide

Abbreviations: QD = once daily.

Table 6-7 Lenalidomide (REVLIMID®) Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Non-Hematologic Adverse Events[68]

Adverse Event (Severity)	Action on Lenalidomide	Further Considerations
Grade 3/4 toxicities judged to be related to lenalidomide	Hold lenalidomide treatment, and restart at the next lower dose level when toxicity has resolved to ≤ Grade 2 during a treatment cycle[68] or to ≤ Grade 1 or patient's baseline condition before initiating the next cycle.	Discontinue lenalidomide if the 5 mg dose is not tolerated
Renal impairment	Dose reduce per lenalidomide package insert/SmPC for impaired renal function	Care should be taken in the elderly as they are more likely to have renal impairment. Monitor renal function regularly in elderly patients and/or patients with renal impairment.
≥ Grade 2 thrombosis/embolism	Hold lenalidomide and start anticoagulation therapy; restart at investigator's discretion after adequate anticoagulation; maintain dose level	See Section 6.10 for anticoagulation recommendations
Angioedema, Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)	Permanently discontinue lenalidomide per package insert/SmPC[68]	
Grade 2/3 skin rash	Hold or discontinue lenalidomide per package insert/SmPC[68]	
Grade 4 exfoliative or bullous rash	Permanently discontinue lenalidomide per package insert/SmPC[68]	

Abbreviations: SmPC = Summary of Product Characteristics.

6.4.4 Dexamethasone-Related Treatment Modification

Dosage adjustments for dexamethasone are outlined in Table 6-8**.** Treatment modifications due to dexamethasone-related AEs are outlined in Table 6-9. Alternative dose modifications may be recommended after discussion with the investigator and Millennium project clinician/designee to maximize exposure of study treatment while protecting patient safety.

Table 6-8 Dose Reduction Steps for Dexamethasone

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
40 mg	20 mg	8 mg	Discontinue dexamethasone

Table 6-9 Dexamethasone–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events[69]

Adverse Event (Severity)		Action on Dexamethasone
Gastrointestinal	Dyspepsia, gastric, or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with histamine-H2 receptor blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, decrease dexamethasone by 1 dose level.
	≥ Grade 3 (or any grade requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease 1 dose level of current dose along with concurrent therapy with histamine-H2 receptor blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Permanently discontinue dexamethasone.
Cardiovascular	Edema ≥ Grade 2 (limiting function and unresponsive to therapy or anasarca)	Intervention indicated (eg, diuretics) as needed and decrease dexamethasone by 1 dose level. If edema persists despite these measures, decrease dose another level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurological	Confusion or mood alteration ≥ Grade 2	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite these measures, permanently discontinue dexamethasone.
Musculoskeletal	Generalized muscle weakness ≥ Grade 2	Decrease dexamethasone dose by 1 dose level. If weakness persists despite these measures, decrease dose further by 1 dose level. Permanently discontinue dexamethasone if symptoms persist.
Metabolic	Hyperglycemia	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite these measures, decrease dose by 1 dose level until blood glucose levels are satisfactory.

6.5 Criteria for Toxicity Recovery Before Beginning the Next Cycle of Treatment

The criteria for toxicity recovery before the patient can begin the next cycle of treatment are as follows:

- ANC ≥ 1,000/mm^3
- Platelet count ≥ 75,000/mm^3, and
- Other clinically significant nonhematologic toxicities ≤ Grade 1 (or to the patient's baseline condition)

Based on attribution of toxicity to a particular drug in the study drug regimen (see Section 6.4), hold the study drug until resolution of toxicity. A patient is to then be restarted on the study drug at the next lower dose. If a patient fails to meet the criteria above for beginning the next cycle of treatment, initiation of the next cycle should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met.

The maximum delay allowed before treatment should be permanently discontinued (except in the case of investigator determined clinical benefit and discussion with the MPI/designee clinician) will be 3 weeks.

6.6 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited while the patient is on the study drug regimen. Note that the excluded concomitant medication information has been updated to reflect the available in vitro metabolism and clinical drug-drug interaction information as of Amendment 2. Please refer to Section 1.4 and the IB for additional details.

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 (Rationale: If there were to be a drug-drug interaction with an inducer, MLN2238 exposure would be decreased.)

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

Excluded medicinal products include St. John's wort.

The following procedures are prohibited while the patient is on the study drug regimen:

- Any antineoplastic treatment other than study drug regimen
- Radiotherapy (note that, in general, the requirement for local radiotherapy indicates disease progression). Palliative local radiotherapy for pain control in a preexisting lesion at baseline may be considered after agreement with the Millennium/designee clinician
- Platelet transfusions to help patients meet eligibility criteria are not allowed

6.7 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care will be available to patients, as necessary. All blood products and concomitant medications received from first dose of the study drug regimen until 30 days after the final dose will be recorded in the eCRFs.

The following medications and procedures are permitted while the patient is receiving the study drug regimen:

- Myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) are permitted. Their use should follow the product label, published guidelines and/or institutional practice.
- Erythropoietin will be allowed in this study, but given the potential increased risk of DVT when erythropoietin is administered concurrent with lenalidomide, the use of erythropoietin should be minimized as much as possible.
- Patients should be transfused with red cells and platelets as clinically indicated.
- Concomitant treatment with bisphosphonates will be encouraged for all patients with evidence of lytic destruction of bone or with osteopenia, according to the American Society of Clinical Oncology Clinical Practice Guidelines or institutional practice in accordance with the product label, unless specifically contraindicated. If bisphosphonate therapy was not started prior to the study start, it should be initiated as soon as clinically indicated.

- Supportive measures consistent with optimal patient care may be given throughout the study.

6.8 Precautions and Restrictions

- When digoxin was co-administered with lenalidomide, the digoxin AUC was not significantly different; however, the digoxin C_{max} was increased by 14%. Periodic monitoring of digoxin plasma levels in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication is recommended during administration of lenalidomide.

- Fluid deficit should be corrected before initiation of treatment and during treatment.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

6.9 Contraception Requirements

It is not known what effects MLN9708 has on human pregnancy or development of the embryo or fetus. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Female patients of childbearing potential (FCBP) and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Definition of FCBP

- All countries except Canada: This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

- Canada: This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone previous bilateral salpingo-oophorectomy or hysterectomy or 2) has not been naturally amenorrheic (amenorrhea following cancer therapy does not rule out

childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months)

All females of childbearing potential must either:

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, for at least 28 days before starting the study drug regimen through 90 days after the last dose of study treatment (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception) OR

- Agree to use 2 reliable methods of contraception, at the same time, for at least 28 days before starting the study drug regimen through 90 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. FCBP 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)
        - Tubal ligation
        - Partner's vasectomy

      Additional effective methods:

        - Condom
        - Diaphragm + spermicide
        - Cervical Cap + spermicide

- Must also adhere to the guidelines of the Revlimid REMS™ (formerly known as RevAssist®) program (US participants), RevAid® program (Canadian participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study

Manual (all other participants who are not using commercial Revlimid supplies). The counseling must be documented.

- Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, the patient should switch to 1 of the effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone

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

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception) OR

- Agree to use effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy, AND

- Must also adhere to the guidelines of the Revlimid REMS™ (formerly known as RevAssist®) program (US participants), RevAid® program (Canadian participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial Revlimid supplies). The counseling must be documented.

6.10 Management of Clinical Events

Prophylaxis Against Risk of Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir or valacyclovir may be initiated as clinically indicated.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with MLN9708. 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 decreased appetite. 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 any drug in the study drug regimen and as needed during treatment to avoid dehydration.

Thromboembolism Prophylaxis

While on lenalidomide, patients should be on routine thromboprophylaxis.[6] Prophylactic therapy with aspirin (70 - 325 mg PO QD, or equivalent dose per country product label [PI or SmPC]) or LMWH (equivalent to enoxaparin 40 mg subcutaneous [SQ] per day) per published standard or institutional standard of care is required for all patients to prevent thromboembolic complications that may occur with lenalidomide-based regimens in combination with dexamethasone (see Section 5.1, inclusion criterion 8 for details on the mandatory use of LMWH).

Nausea and/or Vomiting

Standard antiemetics including 5-hydroxytryptamine 3 serotonin receptor (5-HT3) antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic antiemetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an antiemetic. Fluid deficit should be corrected before initiation of any drug in the study drug regimen, and during treatment.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, 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 deficit should be corrected before initiation of any drug in the study drug regimen, 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 PI.[68,70,71] 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/SmPC.[68]

Rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient and self-limiting, and is typically Grade 1 to 2 in severity. As in any other oncology trial, rash may occur in patients receiving placebo and in patients receiving MLN9708. If rash occurs, consideration should be given to alternate causes of the rash such as concomitant medications, infections, etc.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent [see Section 15.5]) is permitted. Management of a Grade 3 rash may require IV antihistamines or corticosteroids. Administration of MLN9708 (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also per protocol) (see Table 6-3).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines).

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when MLN9708 (or placebo) was given with concomitant medications that are known to cause rash (eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding TEAEs. These severe, potentially life-threatening or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. Additional information regarding these reactions can be found in the IB.

Thrombocytopenia

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. Lenalidomide or study drug administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-1). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura, a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. Thrombotic thrombocytopenic purpura should be managed symptomatically according to standard medical practice.

Neutropenia

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. Growth factor support is not required but may be considered according to standard clinical practice. Lenalidomide or study drug administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

Fluid Deficit

Dehydration should be avoided since lenalidomide is substantially excreted by kidney, and MLN9708 may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with MLN9708, commonly in the setting of the above-noted GI toxicities and dehydration. Fluid deficit should be corrected before initiation of any drug in the study drug regimen and during treatment to avoid dehydration (see Section 6.8).

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with MLN9708. 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) or computed tomography (CT). 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

One case of transverse myelitis has been reported with MLN9708. It is not known whether MLN9708 causes transverse myelitis; however, because it happened to a patient receiving MLN9708, the possibility that MLN9708 may have contributed to transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. If overdose occurs, consider close observation including hospitalization for hemodynamic support. Gastric lavage may be considered if instituted within 1 hour of ingestion of MLN9708 overdose.

6.11 Blinding and Unblinding

To maintain the blind, all study personnel including the investigators, site personnel, study clinicians, and the sponsor will be blinded to the treatment assignments for the duration of the study. When a patient is discontinued from the study drug regimen, the investigator can request to know the patient's actual study drug assignment upon approval from the Millennium clinician/ study clinician designee (contact information is in the Study Manual). The investigator will provide a justification for the request (eg, why knowing the study drug assignment will aid decision making as to the patient's subsequent anticancer treatment or why this information is required to investigate and treat a suspected study drug-related toxicity).

Treatment assignments will be obtained through the interactive voice/ web response system (IXRS) according to the procedures outlines in the Study Manual. Information regarding the treatment assignments will be kept securely at Millennium or designee, per its standard operating procedures. Emergency unblinding, if necessary, will be conducted via the IXRS.

Records of the patient number, the date each drug in the study drug regimen was dispensed, and the treatment assignment will be maintained by the study site. If the treatment assignment must be revealed for the safety of the patient or to treat an AE, the investigator

will contact the Millennium clinician/ study clinician designee. A decision to break the blind must be reached by the Millennium clinician/study clinician designee and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Millennium clinician/ study clinician designee if it is considered to be an emergency by the investigator that requires specific knowledge of the blinded study treatment in order to properly treat the AE/safety issue. If the treatment of the AE/ safety issue is the same regardless of the study drug assignment, the blind should not be broken. In addition, the patient will be discontinued from further study drug administration in this study.

At the time when the study is unblinded, either when planned or before, any changes to the required procedures outlined in the Schedule of Events will be communicated to the investigative sites.

6.12 Description of Investigational Agents

MLN9708 and matching placebo capsules are manufactured by Millennium. The MLN9708 drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg capsules as the active boronic acid. Matched placebo will correspond to each dose strength of MLN9708 and will be identical in size, shape, and color to the corresponding MLN9708 capsule.

The 3 different dose strengths are differentiated by both capsule size and color:

Table 6-10 MLN9708/Placebo Capsules

Dose Strength[a]	Capsule Size	Capsule Color
4.0 mg	Size 3	Ivory
3.0 mg	Size 4	Light Gray
2.3 mg	Size 4	Flesh

a Dose strength for MLN9708. The placebo capsules contain microcrystalline cellulose, talc, and magnesium stearate and are identical in color and size to the corresponding active dose.

For additional details, please see the MLN9708 IB and Pharmacy Manual.

6.13 Preparation, Reconstitution, and Dispensing

Study drug dispensed to the patient for take-home dosing should remain in the blister packaging and carton until the point of use. Refer to the Pharmacy Manual or equivalent storage guidelines. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time; more than 1 cycle of medication may

be dispensed on a case-by-case basis for holidays, travel, or other circumstances upon discussion with the investigator and sponsor's project clinician/designee. Should more than 1 cycle of medication be dispensed, the investigator and/or health care provider must review the proper dosing instructions with the patient to avoid the potential for incorrect self-administration or overdose of medication.

Patients should be instructed to store the medication according to the storage conditions that are outlined in the Pharmacy Manual or equivalent storage guidelines for the duration of each cycle. Patients should be instructed to return their empty cartons to the investigative site, rather than discarding them, as permitted by site policy. 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.

6.14 Packaging and Labeling

For the finished drug product, the capsules are packaged in cold form foil-foil blisters in a child-resistant carton.

The MLN9708 capsules and placebo capsules will be provided by Millennium. The study drug labels will fulfill all requirements specified by governing regulations. The formulation consists of 2.3-, 3.0-, and 4.0-mg capsules for oral administration.

The capsules are individually packaged using cold form foil-foil blisters that are in a child-resistant carton. There are 3 capsules in each wallet/carton.

6.15 Storage, Handling, and Accountability

On receipt at the investigative site, study drug should remain in the blister and carton provided until use or dispensation. All excursions that occur at the site storage or during transportation from depot to the site should be brought to the sponsor'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.

Because MLN9708 is an anticancer drug, as with other potentially toxic compounds, caution should be exercised when handling the study drug. 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 clean-up and during return of broken capsules and powder to minimize skin contract. 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 country, 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 study drug, including that study drug is to be taken as intact capsules.

Please refer to the Pharmacy Manual for additional instructions, including, but not limited to study drug shipping and storage guidelines.

6.15.1 Background Therapies

6.15.1.1 Lenalidomide

Lenalidomide may be supplied by the site or from commercial sources, depending on regional availability as follows:

- US: Subjects will receive lenalidomide through the Revlimid REMS™ (formerly known as RevAssist®) program. Patients in the US must be enrolled into the Revlimid REMS™ program for the procurement of lenalidomide, details for which may be found in the separate Study Manual.
- Canada: Subjects will receive lenalidomide through the RevAid® program. Patients in Canada must be enrolled into the RevAid® program for the procurement of lenalidomide, details for which may be found in the separate Study Manual.
- All other countries: Subjects will receive lenalidomide from the site through supply provided by sponsor. These patients must follow the guidelines for the Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual.

Additional details are provided in the PI/SmPC.[68]

Lenalidomide capsules should be stored at temperatures in accordance with the instructions provided in the manufacturer's PI/SmPC.

6.15.1.2 Dexamethasone

Dexamethasone may be supplied by the site from commercial sources or from the sponsor, depending on regional availability. Additional details are provided in the PI.[69]

Dexamethasone tablets should be stored according to the instructions provided in the manufacturer's PI or on the drug label (if supplied by the sponsor).

6.16 Other Protocol-Specified Materials

No other drugs or ancillary material are supplied for use in this trial.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the Millennium clinician/ study clinician designee, the central laboratory, any additional clinical laboratories, or vendors participating on the study may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

After written informed consent has been obtained, the patient will be assigned an enrollment code (country-, site-, and patient-specific) using IXRS.

Patient eligibility will be confirmed by an MPI/designee clinician before randomization by the investigator into the study. A centralized randomization using IXRS will be used. Patients will be randomized strictly sequentially at a center as they become eligible for randomization. If a patient discontinues from the study, that randomization code will not be reused, and the patient will not be allowed to re-enter the study.

7.4 Study Procedures

Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, EOT, and Follow-Up (PFS and OS [including assessment of PFS2 during OS follow-up]). Tests and procedures during the Treatment Period should be performed on schedule, but occasional changes are allowable (± 2 days or a longer window after discussion with the Millennium project clinician or designee) for holidays, vacations, and other administrative reasons. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing.

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Informed consent may be obtained prior to the 28-day Screening period. Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient, including all current medications, prior radiation, and the patient's current smoking status.

In addition, IMWG diagnostic criteria (Section 15.2) and current ISS staging (Section 15.4) of MM will be determined based on clinical exam and laboratory results.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events. Symptom-directed examinations should include examination of organ

systems related to patient symptoms to document potential AEs, AE severity, or AE resolutions. A baseline (pretreatment) evaluation of PN will be conducted as part of the visit. If PN is present at baseline and within the permitted criteria for study participation (see Section 5.2), the grade must be reported in the eCRF.

7.4.5 Vital Signs

Measurement of vital signs, including temperature, blood pressure, heart rate, respiratory rate, and body weight will be done at the time points specified in the Schedule of Events. Height will only be measured at the Screening visit.

7.4.6 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance scale at the time points specified in the Schedule of Events.

7.4.7 Pregnancy Test

Screening

All countries except Canada: FCBP are required to have TWO medically-supervised negative serum and/or urine pregnancy tests with a sensitivity of at least 25 mIU/mL, even if continuous abstinence is the chosen method of contraception, prior to the first dose of lenalidomide. One test must be obtained within 10 to 14 days and 1 test within 24 hours prior to the start of the study drug regimen at Cycle 1, Day 1. The dates and results of pregnancy tests must be documented.

Canada: FCBP are required to have TWO medically-supervised negative serum pregnancy tests with a sensitivity of at least 25 mIU/mL, even if continuous abstinence is the chosen method of contraception, prior to the first dose of lenalidomide. One test must be obtained within 7 to 14 days, the second within 24 hours prior to the start of the study drug regimen on Cycle 1, Day 1. The dates and results of pregnancy tests must be documented.

Refer to Section 6.9 for definition of FCBP.

On Treatment

FCBP with regular or no menstruation must have a serum or urine pregnancy test weekly, as defined regionally, for the first 28 days and then every 28 days while on treatment (including breaks in therapy), at discontinuation of study treatment, and at Day 28 after the last dose of the study drug regimen. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on study (including breaks in therapy), at discontinuation of treatment, and at Days 14 and 28 after the last dose of treatment. The dates and results of all pregnancy tests must be documented. All patients must follow the lenalidomide PI while on therapy and be counseled about pregnancy precautions, risks of fetal exposure, and other risks in accordance with the Revlimid REMS™ (formerly known as RevAssist®) program (US participants), RevAid® program (Canadian participants), or the Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial supplies).

The Cycle 1, Day 1 pregnancy test may be collected up to 24 hours before dosing. The results must be available and negative before the first dose of the study drug regimen is administered. The date and results must be documented.

Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations. The dates and results of these additional pregnancy tests must be documented.

7.4.8 Concomitant Medications and Procedures

Concomitant medications and therapy will be recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen, with the exception of narcotics and other analgesics, which will be recorded from first dose of study drug until progressive disease (see the Schedule of Events). See Section 6.6 for a list of prohibited concomitant medications and therapies and Section 6.7 for a list of allowed concomitant medications and therapies.

7.4.9 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.10 Enrollment

A patient is considered to be enrolled in the study when he/she has been randomized to study treatment.

Procedures for completion of the enrollment information are described in the Study Manual.

7.4.11 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be conducted at screening and at the times outlined in the Schedule of Events. It may be repeated as clinically indicated during the study at the discretion of the investigator. ECG data to be obtained include PR interval, QRS interval, QT interval, QTc interval, and waveforms.

7.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by a central laboratory. For on study treatment dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must still be sent to the central laboratory in parallel. The central laboratory results will be used for determination of eligibility criteria. Patients may have central laboratory assessments repeated when discrepant results between the central and local laboratories are observed. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Days 8, 15, and 22 dosing, where required. Local laboratory evaluations may be done more frequently at the investigator's discretion, ie, for acute management of TEAEs. Handling and shipment of central clinical laboratory samples are outlined in the Study Manual.

Please consult your central laboratory manual for the turnaround times in obtaining the central laboratory results. The site must allow an adequate amount of time for these samples to be processed and include this in the planning during the Screening period. If the samples have been submitted to the central laboratory but were unable to be processed for technical reasons and the end of the screening window is approaching, the site may submit local laboratory results for consideration by the MPI project clinician or designee. These samples should be repeated and dispatched to the central laboratory before the patient receives their first dose of study treatment. However, when approved by the MPI project clinician or designee, the central laboratory results do not need to be available if the MPI project clinician or designee has approved eligibility based upon local laboratory results.

As the laboratory results may not be available at the initiation of the next cycle, it is not required that these measurements be reviewed before initiating the next treatment cycle unless either of the following applies:

1. The patient has an ongoing toxicity. If the patient has had a toxicity resulting in a dose hold, it is mandatory that safety labs (local or central) are collected AND reviewed before starting the next cycle of treatment.

2. It is required per your local practice to have safety labs reviewed before starting the next cycle of treatment.

Clinical Chemistry, Hematology, and Urinalysis

Blood and urine samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events. Blood samples should be collected prior to administration of any study drugs.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (ANC)

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine*
- Bilirubin (total)
- Urate
- Lactate dehydrogenase
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium
- Thyroid Stimulating Hormone (TSH)

* Creatinine clearance should be determined by using the Cockcroft-Gault Equation (see Section 15.3).

Urinalysis

- Turbidity and Color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Occult Blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes
- Microscopic analysis

7.4.13 Health Utilization Data Collection

During the treatment and the follow-up periods indicated in the Schedule of Events, all medical care encounters since the previous collection will be collected from all patients, regardless of the reason for the medical care encounter. Examples of data to be collected are number and duration of medical care encounters, such as inpatient/outpatient admissions, homecare, and time of work loss.

7.4.14 Quality of Life Assessment (European Organization for Research and Treatment of Cancer)

The QOL assessments (EORTC-QLQ-C30 and MY-20; see Sections 15.9 and 15.10) will be completed by the patient as specified in the Schedule of Events. The EORTC QLQ-30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The time recall period for this instrument is 1 week (the week immediately preceding the assessment).

The MY-20 multiple myeloma module (20-items) has 4 independent subscales, 2 functional subscales (body image, future perspective), and 2 symptoms scales (disease symptoms and side-effects of treatment). This will be administered subsequent to the EORTC QLQ-C30.

These are reliable and valid measures of health-related QOL in patients with cancer and takes about 15 minutes to administer. The instruments consist of a total of 50 items and have been validated and used in many countries.

These QOL assessments must be completed before other assessments are performed or any drug in the study drug regimen is administered.

7.4.15 Pain Assessment

Pain assessments will be performed at study visits as described in the Schedule of Events. Patients who experience new or worsening pain between scheduled visits should be seen at an unscheduled visit, if necessary, or when the next scheduled visit is more than 4 weeks in the future. At the unscheduled visits, pain assessments should be completed and appropriate management instituted. In addition, patients who report new or worsening pain at either a regularly scheduled visit or are seen for pain at an unscheduled visit should have a follow-up

visit 3 to 5 weeks later for confirmation of the pain progression and for appropriate pain management.

The Brief Pain Inventory-Short Form (BPI-SF) will be the principal pain assessment tool for this study. The BPI-SF contains 15 items designed to capture the pain severity ("worst," "least," "average," and "now" [current pain]), pain location, medication to relieve the pain, and the interference of pain with various daily activities including general activity, mood, walking activity, normal work, relations with other people, sleep, and enjoyment of life.

The questionnaire employs a 24-hour recall period. The pain severity items are rated on a 0 to 10 scale, with 0 = no pain and 10 = pain as bad as you can imagine. The PRO key secondary endpoint will be "pain response rate" as measured by the worst pain item (Item 3) in the BPI-SF or analgesic use. The use of the single item, worst pain, is supported by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for assessing pain in clinical trials and by the European Medicines Agency 2003 Guidance on Clinical Investigation of Medicinal Products for Nociceptive Pain issued by the Committee for Proprietary Medicinal Products. In addition, the newly released Food and Drug Administration (FDA) Guidance uses the following example while discussing conceptual frameworks: "The conceptual framework of a PRO instrument may be straightforward if a single item is a reliable and valid measure of the concept of interest (eg, pain intensity)."

At the time of each pain assessment including unscheduled visits, the patient will be queried regarding concomitant use of analgesics, if any, as specified in the Schedule of Events. The patient-recalled amount of analgesic use during the 24 hours prior to pain assessment will be recorded on both the 24-hour analgesic form and concomitant medication eCRFs.

A full BPI-SF instrument will be administered at each of the visits as specified in the Schedule of Events to collect the pain severity, location, and interference information with a 24-hour recall period. This must be completed prior to other assessments or study drug regimen being administered.

Patients will complete the BPI-SF at each visit as specified in the Schedule of Events. Thus, for patients who discontinue study drug before disease progression, the scheduled collection of pain assessment should continue until disease progression.

7.4.16 Utility Measurement

The EQ-5D consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). The EQ VAS records the respondent's self-rated health on a 20-cm vertical, visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D will be administered as specified in the Schedule of Events.

7.4.17 Skeletal Survey

A complete skeletal survey, using roentgenography, will be performed at screening (within 8 weeks prior to randomization) and a minimum of every 12 months from randomization until disease progression in all patients until PFS significance has been claimed in this study. If at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions, a repeat of the skeletal survey should be performed. For imaging of symptomatic sites, plain films may be obtained for additional clarity.

At the discretion of the investigator and where regionally permitted, computed tomography (CT) scan, a positron emission tomography-computed tomography (PET-CT) scan, or whole body MRI may be done at screening in place of a skeletal survey, provided that the same modality for assessment is used throughout the study.

7.4.18 Skeletal-Related Events

SREs, defined as new fractures (including vertebral compression fractures), irradiation of or surgery on bone, or spinal cord compression, will be captured from the start of the study treatment through death at the time points listed in the Schedule of Events until PFS significance has been claimed in this study.

7.4.19 Bone Mineral Density

DEXA scans will be done of the lumbar spine and femoral neck at screening (the DEXA scan does not need to be repeated if already performed within 8 weeks of randomization), 6 months, 1 year, and then annually (± 4 weeks at the corresponding study visit to approximately 6 or every 12 months of treatment) until progressive disease, as indicated in the Schedule of Events.

7.4.20 Radiographic Disease Assessments

For patients with documented extramedullary disease, other assessments and scans such as a CT, PET-CT or MRI scan may be required to better delineate the sites and measurements of extramedullary disease. Follow-up scans should use the same imaging modality used at screening (within 8 weeks of randomization) at the time points specified in the Schedule of Events, until PFS significance has been claimed in this study.

All follow-up scans should use the same imaging modality used at screening.

Radiographs will be analyzed locally and reports maintained with the patient record for review during monitoring visits.

7.4.21 β2-Microglobulin

A blood sample will be collected at screening for serum β2-microglobulin testing. A sample for the central laboratory is required. A sample may additionally be collected by the local laboratory. Stratification by ISS stage 1 or 2 vs 3 will be conducted using central laboratory results. These results must be available prior to randomization.

7.4.22 Quantification of M-Protein

A blood sample and urine sample will be obtained at screening and at the time points specified in the Schedule of Events until PFS significance has been claimed in this study. If the screening test was performed more than 14 days before the first dose, the test will be repeated at baseline in the central laboratory.

Central laboratory results must be utilized for eligibility assessments, per guidance noted in Section 7.4.12.

7.4.23 Quantification of Immunoglobulin (Ig)

Blood samples for quantification of immunoglobulins (IgM, IgG, IgA) will be obtained as specified in the Schedule of Events until PFS significance has been claimed in this study. Quantitative IgD and IgE will be done at screening (and baseline if necessary) only for all patients. For the rare patient with IgD or IgE multiple myeloma, the quantitative test for that antibody will be followed at the same time points throughout the treatment period and PFS follow-up period as quantitative Igs (in addition to quantitative IgM, IgG, and IgA).

Central laboratory results must be utilized for eligibility assessments, per guidance noted in Section 7.4.12.

7.4.24 Serum Free Light Chain Assay

A blood sample for serum free light chain assay will be obtained at the time points specified in the Schedule of Events. Central laboratory results must be utilized for eligibility assessments, per guidance noted in Section 7.4.12.

7.4.25 Immunofixation of Serum and Urine

Serum and urine samples will be obtained at the time points specified in the Schedule of Events. Central laboratory results must be utilized for eligibility assessments, per guidance noted in Section 7.4.12.

7.4.26 Bone Marrow Evaluation

Central Lab Evaluation

Molecular Analyses, Cytogenetics, and Minimal Residual Disease

The sample of the bone marrow aspirate obtained at screening (within 8 weeks of randomization) will be used for molecular analyses and for evaluation of cytogenetics that will cover a panel of high-risk abnormalities including the following: amp(1q21), t(4;14), t(14;16), and del(17p). CCI [redacted]. This sample will be submitted to a central laboratory (See Study Laboratory Manual for sample handling and shipping instructions). The first or second pull of the bone marrow aspirate is the preferred specimen to be sent to the central lab for this analysis.

A bone marrow aspirate will be collected for assessment of MRD in all patients suspected to have reached CR anytime during the entire conduct of the study. In addition, a second bone marrow aspirate for MRD assessment will be collected at Cycle 18 for only patients who have maintained a CR until that point (this sample can be collected up to 4 weeks after Cycle 18). If a patient has had MRD testing because of a suspected CR within 2 cycles of Cycle 18, then this repeat MRD assessment does not need to be performed.

Samples are required to be sent to a central lab for analysis. These samples will be processed according to the Laboratory Manual.

An optional aspirate for molecular analysis will also be collected at the time of disease relapse only if the patient had previously responded to study drug regimen and consents to this procedure. This sample may be collected at the time of PD confirmation, at the End of Treatment visit, or prior to starting a new therapy and will be sent to the central laboratory for analysis.

Local Lab Evaluations

Disease Assessment

A bone marrow aspirate will be obtained at screening (within 8 weeks of randomization) to assess the patient's eligibility in accordance with the IMWG diagnostic criteria (Section 15.2). During the study, a bone marrow aspirate sample should be obtained to confirm a CR when the patient has negative immunofixation serum and urine and/or disappearance of any soft tissue plasmactyoma. To confirm a stringent CR, the bone marrow evaluation must demonstrate the absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry. These samples will be analyzed by the local laboratory.

A bone marrow biopsy can additionally be performed per local standards for disease assessments.

Cytogenetics

A bone marrow aspirate sample must be submitted to a central laboratory for analysis of cytogenetics, including amp(1q21), t(4;14), t(14;16), and del(17p). An optional bone marrow aspirate or bone marrow sample may also be submitted for cytogenetics to be analyzed locally, including amp(1q21), t(4;14), t(14;16), and del(17p), according to local standards, if the site has capability to perform analysis and there is sufficient sample available. The central laboratory cytogenetic results will be utilized for study analysis, whereas local laboratory cytogenetic results (where available) will only be utilized in instances when central laboratory results are not available.

7.4.27 Response Assessment

Patients will be assessed for disease response according to the IMWG uniform response criteria, version 2011 (see Section 15.11).[72]

Response assessments are made on the basis of central laboratory data and should occur every cycle during the treatment period (until disease progression is confirmed) until PFS significance has been claimed for this study. At that time, central efficacy and investigator

assessments for protocol purposes will be stopped except for investigator assessment of PFS2. For patients who discontinue treatment before disease progression, disease response should occur every 4 weeks during the PFS follow-up period until disease progression is confirmed or the patient is started on another anticancer therapy (see the Schedule of Events), or until PFS significance has been claimed for the study.

The MPI/designee clinician will confirm the investigator assessment of PD prior to the investigator taking the patient off treatment. A treatment discontinuation form must be submitted and approved prior to removing a patient from study treatment for disease progression, toxicity, or any other reason.

Patients who go on to receive a subsequent line of anticancer therapy will be further evaluated for disease response (at minimum disease progression) to confirm disease progression for determination of PFS2. Response assessments will be made using local laboratory results, and the frequency will be determined by the investigator (recommended every 12 weeks). Response assessments, including the treatment received and date of second disease progression, should be reported in the eCRF every 12 weeks as part of the OS follow-up period assessments.

Response categories are as follows:

Table 7-1 Response Assessment

Complete response	CR
Subcategory: stringent complete response	*sCR*
Partial response	PR
Subcategory: Very good partial response	VGPR
Stable disease	SD
Progressive disease	PD

CR must be confirmed with follow-up assessments 4 weeks (1 cycle) following the first observation of CR of serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), immunofixation of blood and urine, serum free light chains, and radiological assessment of soft tissue plasmacytoma if applicable, as outlined in Section 15.11. One bone marrow assessment has to occur to document CR; no second bone marrow confirmation is needed.

Please note that in order to determine a response of sCR, bone marrow immunohistochemistry or 2- to 4- color flow cytometry for kappa/lambda ratio should be performed for all patients suspected to be in CR to meet this response category's requirements.

Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these 2 tests and not by the free light chain assay. Free light chain response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of stringent CR.

7.4.28 Pharmacokinetic Measurements

Plasma concentrations of the complete hydrolysis product of MLN9708 (MLN2238) will be measured using a validated LC/MS/MS assay.

Details regarding the preparation, handling, and shipping of the pharmacokinetic samples are provided in the Study Manual. Blood samples (3 mL) for the determination of plasma concentrations of MLN2238 (the complete hydrolysis product of MLN9708) will be collected during Cycles 1 through 12. Samples are to be collected at the time points specified in the MLN9708 Pharmacokinetic Sampling Schedule immediately following the Schedule of Events.

7.4.29 Blood Sample for Biomarker Analysis

CCI

[redacted]

CCI

[redacted]

7.4.30 Treatment Beyond 18 Cycles

Patients may continue to receive the study drug regimen of 4.0-mg study drug + LenDex for 18 cycles (approximately 18 months), or until PD or unacceptable toxicity, whichever comes first. After 18 cycles, patients will continue treatment in the same randomization arm on the same schedule with modified dose levels of study drug and lenalidomide until disease progression to mitigate toxicities (see Table 4-1). Dose modifications should be made based on prior dose modifications during the first 18 cycles of treatment (see Table 6-4, Table 6-6, and Table 6-8).

7.4.31 Follow-up Assessments (PFS, PFS2, and OS)

Patients who stop treatment for any reason other than progressive disease will continue to have PFS follow-up visits. See the Schedule of Events for appropriate assessments. The PFS follow-up should occur every 4 weeks until disease progression is confirmed or the patient is started on another anticancer therapy, whichever comes first.

Patients who stop treatment due to progressive disease will subsequently start OS follow-up assessments/visits. The OS follow-up should be conducted every 12 weeks after documented progressive disease until death or termination of the study by the sponsor. All subsequent antineoplastic therapies will be recorded until the patient dies. Patients who go on to receive a subsequent (second) line of anticancer therapy will be evaluated for disease response (at minimum disease progression) to confirm disease progression for determination of PFS2. Response assessments will be made using local laboratory results, and the frequency will be determined by the investigator (recommended every 12 weeks). The treatment received and date of second disease progression should be reported in the eCRF every 12 weeks as part of the OS follow-up period assessments.

During the OS follow-up, assessments can be made over the phone and do not require a clinic visit. Data may be collected by methods that include but are not limited to telephone, e-mail, mail, and social security indexes.

Information for new primary malignancy should be collected during the study, including the PFS and OS follow-up periods.

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. In addition, new primary malignancies that occur during the follow-up periods, irrespective of causality to study drug regimen, must be reported to the Millennium Department of Pharmacovigilance or designee.

Refer to Section 10 for details regarding definitions, documentation, and reporting of SAEs.

7.5 Unscheduled Visits

Unscheduled visits may occur between treatment cycles as required. At unscheduled visits, the BPI-SF and CCI data should be captured. Other assessments may be performed as clinically indicated at the discretion of the investigator.

7.6 Study Compliance

Each drug in the study drug regimen will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing.

7.7 Completion of Treatment

Patients will be considered to have completed study treatment if they receive the study drug regimen until disease progression or until discontinuation for unacceptable toxicity, withdrawal of consent, or death. Quality Review by a MPI/designee clinician is required prior to discontinuing a patient from treatment or stopping disease assessments for progressive disease. A treatment discontinuation form must be submitted and approved prior to removing a patient from study treatment for disease progression, toxicity, or any other

reason. Patients will attend an EOT visit 30 days (+1 week) after receiving their last dose of the study drug regimen unless next-line therapy is started before 30 days after the last dose of study drug, in which case the EOT visit should occur before the start of the next-line therapy. Patients will continue to be followed for other follow-up assessments specified in the Schedule of Events. Refer to the Schedule of Events for End of Treatment visit assessments.

7.8 Completion of Study

Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study.

7.9 Discontinuation of Treatment With the Study Drug Regimen, and Patient Replacement

Treatment with the study drug regimen must be discontinued for pregnancy. Treatment with the study drug regimen may be discontinued for any of the following reasons:

- Adverse event (including SAE)
- Protocol violation
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Pregnancy (patient must be discontinued)
- Other

Once the study drug regimen has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

7.10 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Study terminated by sponsor

- Withdrawal by patient
- Lost to follow-up
- Other

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

Details for the analyses will be provided in the statistical analysis plan (SAP). The SAP will be written by Millennium and will be finalized prior to the formal IA.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

8.1.1 Determination of Sample Size

The primary objective of this study is to determine if MLN9708 plus lenalidomide and dexamethasone improves PFS compared with placebo plus lenalidomide and dexamethasone in patients with newly diagnosed MM. The study will not be stopped after the PFS analysis, however, even if a significant PFS is observed, in order to obtain an adequate statistical power for OS.

The total sample size of approximately 701 patients was calculated based on maintaining 80% power to test the OS. The study is also adequately powered to test PFS. There are 2 planned IAs and 1 FA.

Assuming a hazard ratio of 0.70 (median PFS of 25 months in control arm versus 35.8 months in treatment arm), 370 PFS events will be needed (92% power and 2-sided alpha of 0.04) with up to 2 planned PFS analyses conducted at the first IA and potentially second IA of this study using the Gamma(-1) alpha-spending function.

The first IA will be performed when approximately 326 PFS events have occurred. This is expected to occur approximately 45 months after the first patient is enrolled, including a 27-month enrollment period and additional 18-month follow-up from the last patient.

If the test for PFS in the ITT population is statistically significant at the first IA, this will be the FA for PFS for statistical testing purposes, and the second IA will assess OS when approximately 250 death events have occurred.

If the test for PFS in the ITT is not statistically significant at the first IA, then the second IA will assess PFS and OS when approximately 370 PFS events have occurred. In addition, in such a case, PFS will be tested at IA2 in 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21).

For the final OS analysis, the total event size calculation will be based on the adaptive sample size re-assessment approach.[66,67] The minimum event size of CCI death events is based on an optimistic assumption of a hazard ratio of 0.72 (median survival of 50 months in the control arm vs 69.4 months in the treatment arm) with 80% power at a 2-sided 0.05 level of significance. The O'Brien-Fleming alpha spending function (the Lan-DeMets method) will be used to calculate the significance boundary based on observed number of death events in each IA with a total of 320 OS events for the FA. In the second IA, if OS significance is not claimed, the conditional power based on OS will be calculated. If the conditional power falls in the favorable zone or unfavorable zone, the FA of OS with approximately 320 events will remain unchanged. If the conditional power falls in the promising zone, the event size will be determined according to a prespecified sample size adaptation rule, with an event cap of ~400 OS events. No futility analysis will be performed in the study.

The sample size adaptation rule is a prespecified stepwise function to avoid the back calculation problem resulting from one sample size corresponding to either barely promising or highly promising interim results. The sample size adaptation rule will be designed by the sponsor's independent design statistician and approved by the sponsor's head of

biostatistics. Neither the independent design statistician nor the head of biostatistics is involved in the study conduct.

The adaptation rules will be outlined in a separate document and will not be accessible to the sponsor's study team until completion of the study. The rules will be available only to the sponsor's independent design statistician, the sponsor's head of biostatistics, the IDMC, and the statistics representative on the sponsor's executive committee (if different from the sponsor's head of biostatistics).

8.1.2 Randomization and Stratification

Randomization scheme will be generated by an independent statistician at Millennium who is not on the study team. Prior to dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an IXRS.

Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms, stratified by: age (< 75 years vs ≥ 75), ISS (stage 1 or 2 vs stage 3), and BPI-SF worst pain score (< 4 vs ≥ 4) at screening.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

Safety population: The safety population is defined as all patients who receive at least 1 dose of any study drug. Patients will be analyzed according to the treatment actually received. That is, those patients who are randomized to the active arm but receive the regimen in the control arm will be included in the control arm; those patients who are randomized to the control arm but receive the regimen in the active arm will be included in the active arm for safety analyses.

Intent-to-Treat (ITT) population: The ITT population is defined as all patients who are randomized. Patients will be analyzed according to the treatment they are randomized to receive, regardless of any errors of dosing.

Per-Protocol (PP) population: The PP population is a subset of the ITT population. The PP population consists of all patients who do not have major protocol violations, as determined by the study clinician, who is blinded to study drug assignment. All decisions to exclude patients from the PP population will be made before the unblinding of the study.

Response-Evaluable population: The response-evaluable population is defined as patients who have measurable disease at baseline, who receive at least 1 dose of any study drug, and have at least 1 postbaseline response assessed by an IRC.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. For patient reported outcomes data, primarily missing data imputation will be based on published instrument specific methods. Other missing data imputation methods, such as last observation carry forward and multiple imputation methods, may be explored as sensitivity analyses for patient reported outcomes data.

For the key secondary endpoints CR rate, missing value is defined as no post-baseline response assessment either due to lost to follow-up or withdrawal by patient. In the primary analysis, if the response assessment in either arm is missing on comparing response rates, it will be counted as a failure (non-responder) instead of a missing value. The procedure to deal with missing data in the primary analysis for the pain response rate will be using the same method as CR rate.

8.1.5 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, gender, race, weight, baseline disease characteristics, and other parameters, as appropriate.

8.1.6 Efficacy Analysis

A closed sequential testing procedure will be used to test the primary endpoints and all 3 key secondary endpoints with the following testing order:

1. PFS (primary endpoint) in the ITT population at the first or both IAs (see Section 8.1.1) and PFS at IA2 in 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21);

2. OS (first key secondary endpoint) at the IAs or FA;

3. CR rate (second key secondary endpoint) at the IAs or FA; and

4. pain response rate (third key secondary endpoint) at the IAs or FA.

OS will be tested at the IAs or FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). CR rate will be tested at the same alpha level as that for OS whenever OS reaches statistical significance. Pain response rate will be tested at the same alpha level as that for CR rate whenever CR rate reaches statistical significance. Due to the closed sequential testing property, the family-wise type I error is strongly controlled for both the primary endpoint and key secondary endpoints (see Section 8.1.10).

All other efficacy endpoints will be tested at a 2-sided alpha level of 0.05.

8.1.6.1 Analyses for Primary Efficacy Endpoints

The analysis of primary endpoint, PFS, will be based on the IRC-assessed progression data. PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first. Patients without documentation of PD will be censored at the date of last response assessment that is stable disease (SD) or better.

A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The Kaplan Meier (K-M) survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Sensitivity analyses for PFS include:

1. PFS assessed by investigator will be analyzed in the ITT population

2. PFS assessed by IRC will be analyzed in the per protocol population

PFS assessed by IRC using different censoring mechanisms will be analyzed in the ITT population, for example, not censoring for patients who discontinue treatment and go on alternative antineoplastic therapy. Details of different censoring approaches will be included in the SAP.

Subgroup analyses will be performed for PFS relative to baseline stratification factors, demographic data, such as sex, race, and age, and disease characteristics, such as type of prior regimen.

8.1.6.2 Analyses of Key Secondary Efficacy

In addition to the primary comparison of PFS, there are 3 key secondary endpoints, which will be tested sequentially.

Overall Survival

OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed based on the ITT population.

A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to OS in IAs, and Cui-Hung-Wang (CHW) test statistics will be used in FA testing to control the Type I error. The test significance level at the IAs and FA is decided by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Subgroup analyses will be performed for OS relative to baseline stratification factors, demographic data such as sex, race, age, and disease characteristics such as type of prior regimen.

CR Rate

The CR rate is defined as the proportion of patients who achieve CR assessed by an IRC relative to the ITT population during the treatment period. If the response assessment in either arm is missing on comparing CR rates, it will be counted as a failure (non-responder) instead of a missing value.

Stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare CR rates between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of odds ratio. The odds ratio and its associated 95% CIs will be presented.

Pain Response Rate

Pain response is defined as the occurrence of at least a 30% reduction from baseline in BPI-SF worst pain score over the last 24 hours without an increase in analgesic use for 2 consecutive measurements ≥ 28 days apart.

Pain response rate will be analyzed in patients with baseline worst pain score ≥ 4 in the ITT population. Pain response rate is the proportion of patients who have a pain response and will be summarized by treatment groups. If the pain assessment in either arm is missing on comparing pain response rates, it will be counted as a failure (non-responder) instead of a missing value. The stratified CMH test will be used to compare the 2 treatment arms. In addition, the absolute treatment difference in pain response rate will be provided, along with 95% CI.

Additional exploratory analysis of cumulative distribution function of worst pain score change from baseline will also be conducted.

8.1.6.3 Analyses of Other Secondary Efficacy Endpoints

Other secondary efficacy parameters include overall response rate (ORR), TTR, time to progression, duration of response, PFS2, and OS and PFS in high-risk population defined by del(17p), amp(1q21), and translocation t(4;14) and t(14;16).

Disease response-related endpoints will be analyzed using IRC-assessed response rate.

ORR

ORR is defined as the proportion of patients who achieved PR or better relative to the ITT population. ORR will be analyzed based on the ITT population using the method similar to that used in the CR rate analysis.

Time to Response

Time to response is defined as the time from randomization to the first documentation of PR or better. Time to response for responders will be summarized descriptively.

Time to Progression

TTP is defined as the time from the date of randomization to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the

date of last response assessment that is SD or better. TTP will be analyzed based on the ITT population using the similar method as PFS.

Duration of Response

DOR is defined as the time from the date of first documentation of a PR or better to the date of first documentation of PD for responders. Responders without documentation of PD will be censored at the date of last response assessment that is SD or better. DOR will be summarized descriptively using the Kaplan-Meier method.

Progression-free Survival 2

PFS2 is defined as the time from the date of randomization to the date of second documentation of PD or death due to any cause, whichever occurs first. The second PD should occur during or after the second line of antineoplastic therapy following study treatment but before the third line of therapy. Patients who do not have documented PD will be censored at the date of last response assessment which is SD or better. PFS2 will be analyzed by the treating physician/ investigator using the IMWG response criteria, based on the ITT population using the similar method as PFS.

OS and PFS in High-Risk Population

OS and PFS in a high-risk population, defined as patients carrying del(17p), amp(1q21), translocation t(4;14), or t(14;16) will be analyzed using the similar method as PFS and OS in ITT population.

8.1.7 Analyses of Patient-Reported Outcomes and Health Economics

8.1.7.1 Patient-Reported Outcomes Analysis

PRO assessments using the EORTC QLQ-C30 and the MY-20 will be analyzed using the ITT population. The analysis will be performed on summary scores as well as on subscales and individual symptoms.

Differences between treatment groups in the EORTC QLQ-C30 and MY-20 scores will be evaluated using published minimally important difference (MID) values. Specific interest centers on physical functioning, global quality of life summary scores, and individual item scores for fatigue, nausea/vomiting, pain, dyspnea, appetite loss, and constipation/diarrhea.

The main endpoint for the PRO analysis will be the global health status/quality of life subscale of the EORTC QLQ-C30 and MY-20. The change in PRO scores between baseline

and each postbaseline assessment will be described overall and according to the response to treatment. The other PRO endpoints include the remaining EORTC QLQ-C30 and MY-20 subscale and individual item scores. The change in scores will be presented using cumulative frequency distribution figures.

The analysis of PRO scores will be performed as a repeated-measures analysis using all available time points. The analysis will use mixed model analysis of variance.

8.1.7.2 Health Economics Analysis Using Medical Resource Utilization and Utility

EQ-5D scores will be summarized in descriptive statistics for treatment arms.

Health Utilization data will be summarized in descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities by patient and care-giver for treatment arms.

8.1.7.3 Pain

Additional analyses on pain beyond the key secondary endpoint of pain response rate include:

- Time to pain response, as assessed by the time from randomization to initial response classification
- Time to pain progression, as assessed by the time from randomization to initial pain progression
- Duration of pain response, measured as the time from the first documented pain response to the first documented pain progression classification

Time to pain progression and duration of pain response will be compared using the stratified log-rank test between the 2 treatment groups. An unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment arm. Time to pain response will be summarized descriptively for pain responders.

Pain progression is defined as the occurrence of 1 of the following and confirmed by 2 consecutive evaluations **(**To qualify as progression, the patient must have a BPI-SF worst pain score ≥ 4 during pain progression):

- A ≥ 2 point and 30% increase from baseline in BPI-SF worst pain score without an increase in analgesic use, or

- A 25% or more increase in analgesic use from baseline without a decrease in BPI-SF worst pain score from baseline

Analgesic use change can be increased, stable or decreased, as specified in the SAP.

A sensitivity analysis will be conducted on pain progression without confirmation by 2 consecutive assessments. Confirmation is not required if surgical treatment for pain, palliative radiation for pain, or subsequent antineoplastic therapy has been receive prior to a confirmatory assessment (refer to Table 15-2 for a list of Step II and III analgesics). In addition, the pain scores will be summarized by treatment group.

8.1.8 Pharmacokinetics and Biomarkers

8.1.8.1 Pharmacokinetic Analysis

PK data collected in this study will contribute to population PK analyses. These analyses may include data from other MLN9708 clinical studies and the analysis plan for the population PK analysis will be separately developed and reported.

8.1.8.2 Biomarker Analysis

CCI

[redacted]

CCI

[redacted]

8.1.8.3 Minimal Residual Disease Analysis

The absence of minimal residual disease (MRD negativity) will be tested in all patients who achieve a CR, using bone marrow aspirates. The frequency of MRD negativity, in each treatment arm, will be determined, and its association with TTP, PFS, and OS will be evaluated.

8.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to the study drug regimen and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug regimen and through 30 days after the last dose of study drug regimen will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients)

- SAEs

A listing of treatment-emergent AEs resulting in study drug regimen discontinuation will be provided.

Development of new or worsening of existing SREs (eg, new fractures [including vertebral compression fractures], irradiation of or surgery on bone, or spinal cord compression) from baseline through the development of PD will be summarized and presented.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG performance scores will be summarized using a shift table.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the MLN9708 safety profile.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Two types of incidence rates will be calculated for the safety population based on the new primary malignancy assessment:

- Incidence proportions, defined as the percentage of the subjects reporting any new primary malignancy in the safety population with available information
- Incidence rates, defined by the number of the subjects reporting any new primary malignancy divided by the total duration of follow-up (patient-years = pt-yrs) in the safety population with available information up to the onset of new primary malignancies

For incidence proportions, the relative risks, defined as the ratio of incidence proportions between the 2 randomized treatment groups, were provided along with their 95% CIs. For incidence rates, the relative risks, along with their 95% CIs, will be calculated using an exponential regression model for lifetime data (assuming constant hazards).

Due to the distinct nature of hematologic and nonhematologic neoplasms, as well as the emerging signals of new primary malignancies for immunomodulating agents, analyses of new primary malignancies may be performed separately for hematologic and non-hematologic malignancies.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN9708.

8.1.9.1 Time to Resolution and Improvement of Peripheral Neuropathy Events

Peripheral neuropathy is defined as the treatment emergent adverse event in the high-level term of peripheral neuropathies NEC according to MedDRA.

A PN event is considered as resolved if its final outcome is resolved with no subsequent PN event of the same preferred term occurring on the resolution date or the day before and after. A PN event is considered as improved if the event improves from the maximum grade. That is, all the grades recorded after the maximum grade is less than the maximum grade.

Time to resolution and time to improvement are to be defined for each PN event. Time to resolution is defined as the time from the initial onset date (inclusive) to the resolution date for resolved events. Time to improvement is defined as the time from the initial onset date (inclusive) of the maximum grade to the first onset date that the toxicity grade is below the maximum grade with no higher grade thereafter, or the resolution date, whichever occurs first.

Time to improvement and time to resolution of PN events will be summarized by outcome (improvement or resolution) using the Kaplan-Meier method. The K-M survival curve and K-M medians (if estimable), along with their 2-sided 95% CIs, will be presented. This analysis is event based, thus 1 subject could contribute multiple observations if the subject has more than 1 PN event.

The analysis may be conducted for patients with any PN events or those with ≥ 2 PN events or those ≥ 3 PN events, respectively, if data permits.

8.1.10 Interim Analysis

There are 2 planned IAs. The first IA will be performed when approximately 326 disease progression/death events have occurred. This IA is expected to occur approximately 45 months after the first patient is enrolled. If the test for PFS in the ITT population is statistically significant at the first IA, this will be the FA for PFS for statistical testing purposes, central efficacy and investigator assessments of disease response for protocol purposes will be discontinued (except for investigator assessment of PFS2) given that the primary endpoint has been met, and the second IA will be conducted for OS when approximately 250 death events have occurred. If the test for PFS does not reach statistical significance at IA1 in the ITT population, PFS will be tested in both the ITT population and in 3 prespecified subgroups, as described below.

The subgroup testing strategy approach includes 2 major components: a) preservation of the ability to detect the overall treatment effect using a reduced overall significance level of $\alpha_1 = 0.04$, which will be used for the ITT population, and b) test of treatment effect for the 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21). Subgroup testing will be conducted using the remaining $\alpha_2 = 0.01$ and the Hochberg procedure for multiplicity correction (refer to the appendix in the SAP for proof of strong control of the Type I error rate). Because the size of the treatment effect may be substantially greater in a prespecified subgroup than in the overall study population, analysis of patients in each subgroup at a stringent significance level may still provide a statistically significant outcome. The detailed statistical design schema is presented in Figure 8-1.

Figure 8-1 Schematic of Statistical Plan

For the testing of PFS in the ITT population, the Gamma(-1) alpha spending function will be used to calculate the significance boundary based on the observed number of PFS events with total alpha=0.04. The first IA will be performed when approximately 326 PFS events have occurred. This will be the first analysis for PFS for statistical testing purposes. If the test is statistically significant, then this analysis will be the FA of PFS for statistical testing purposes. No subsequent PFS testing will be conducted, and central efficacy and investigator assessments of disease response for protocol purposes will be discontinued except for the investigator assessment of PFS2 (see the Schedule of Events). In this scenario, the second IA will be for OS testing when approximately 250 death events have occurred and will determine whether the final number of OS events might be increased.

If the test for ITT PFS is not statistically significant at the first IA, response assessments will continue, and PFS testing in the ITT and subgroup populations will be conducted in parallel at the second IA, when approximately 370 PFS events have occurred (rather than the previous study design of 435 PFS events); this will be the FA of PFS for statistical testing purposes. If the test for PFS is significant at the second IA, OS will be tested, and determination of whether the final number of OS events will be increased from 320 to up to

400 will occur. If the test for PFS in the second IA is not statistically significant in any population (the ITT or any of the 3 subgroups), the study will be stopped.

Because at the time of this amendment, the boundary for ITT PFS at IA1 has already been calculated based on 328 PFS events observed at IA1, 435 PFS events targeted at PFS final analysis, and the Gamma(-1) alpha-spending function, this boundary will not be changed. However, the boundary for ITT PFS at IA2 (final analysis of ITT PFS) will be calculated based on the observed number of PFS events at IA2 in order to spend what is left of the overall alpha-level 0.04 for ITT. The final boundaries at IA1 and IA2 will not approximate a Gamma(-1) function, but type I error will remain protected under the flexible alpha-spending approach (see appendix in the SAP for more details).

For the testing of OS, alpha spending for IA1 and IA2 will always be based on the observed events (information fraction) using alpha=0.04 with a different adjustment of critical value at OS FA testing (CHW test statistics [67] will be used for the primary analysis of OS at FA) based on the following scenarios:

1. If ITT PFS is significant in IA1, then ITT OS will be tested in the FA with a total alpha of 0.04; there is no test on subgroup PFS.
2. If ITT PFS is not significant in IA1, then parallel testing of the ITT population PFS and the subgroup populations PFS will occur in IA2:
    a. If the ITT population's PFS is significant and at least 1 subgroup is not significant, then the ITT population's OS will be tested at FA using a total alpha of 0.04.
    b. If the ITT population's PFS is significant and all 3 subgroup populations' PFS are significant, then the ITT population's OS will be tested at FA with a total alpha of 0.05.
    c. If the ITT population's PFS is not significant and at least 1 subgroup population's PFS is significant, then no formal ITT OS testing will be conducted.

The family-wise error rate for the 4 null hypotheses for PFS and the 1 hypothesis for OS for the overall study population is controlled using a prespecified, 2-sided 0.05 level of significance.

The proof of strong control of the Type I error rate for testing PFS and OS in the ITT population and PFS in the subgroup populations is shown in the appendix in the SAP. For the other 2 key secondary endpoints, the CR rate will be tested at the same alpha level,

instead of the same critical value, as that of the OS analysis when OS reaches statistical significance. The pain response rate will be tested at the same alpha level as that of the CR rate analysis when the CR rate reaches statistical significance. Because of the closed sequential testing property, the family-wise error rate is strongly controlled for both the primary endpoint and the 3 key secondary endpoints [78].

The IAs will be conducted by the independent statistical center (ISC) and presented for review to the IDMC. During the closed session of the IDMC meeting, the IDMC will compare the conditional power for OS based on the interim results with the prespecified sample size and primary endpoint adaptation rules and recommend to the sponsor executive committee the final adaptation decision. This recommendation will be documented in the IDMC closed meeting minutes.

9. STUDY COMMITTEES

9.1 Independent Review Committee

An IRC will review all disease evaluation data from the study and determine disease status (response and progression, including PFS follow-up period but does not apply to PFS2 assessment). Data from the IRC will not be provided back to the investigator during the conduct of the study.

9.2 Independent Data Monitoring Committee

An IDMC supported by an independent statistician will review safety and efficacy data at 1 planned interim analysis. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on the IDMC recommendation, Millennium will notify the appropriate regulatory authorities. In addition, the IDMC will periodically review safety data at regularly scheduled meetings prespecified in the IDMC charter. As part of the IDMC safety monitoring, this committee will receive reports of all cases of new primary malignancies occurring during the trial.

The first formal safety review will occur after approximately 60 subjects (30 in each arm) have been randomized and receive at least 1 cycle of study treatment. Subsequently, periodic safety reviews will also occur as prespecified in the IDMC charter.

Study accrual will not be interrupted due to the scheduled safety reviews. The IDMC or MLN9708 study team may request an ad hoc meeting for any reason, including a significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, subject incidence rates of AEs (including all serious AEs, treatment-related AEs, serious treatment-related events, and events requiring the discontinuation of study drug) will be tabulated by System Organ Class, preferred term, and severity grade. Listings and/or narratives of "on-study" deaths and other serious and significant AEs, including any early withdrawals due to AEs, will be provided. Records of all meetings will be archived. The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Millennium. Further details will be provided in the IDMC charter.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Event Definition

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

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.

10.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. 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; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[79] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however,

may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by emailing or faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[79] The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs. AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug, but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRF. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). In addition, all cases of new primary malignancy that occur during the follow-up periods must be immediately reported to the Millennium Department of Pharmacovigilance or designee, irrespective of causality to the study drug regimen, from the first dose of the study drug regimen through death or until termination of the study by the sponsor, whichever comes first. The IDMC will also receive reports of all cases of new primary malignancies occurring during the trial.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on study drug or within 90 days of the patient's last dose of study drug are considered immediately reportable events. Study drug is to be discontinued immediately. The sponsor must also be contacted immediately by emailing or faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to CCI [redacted] (see Section 10.2) immediately by facsimile or other appropriate method, using the Pregnancy Initial Report Form or approved equivalent form. The female patient should be referred to an obstetrician-

gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. The pregnancy must be followed for the final pregnancy outcome.

The investigator will follow the female subject until completion of the pregnancy and must notify CCI [redacted] immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to CCI [redacted] immediately by facsimile or other appropriate method within 24 hours of the investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the investigational product should also be reported to CCI [redacted] immediately by facsimile or other appropriate method within 24 hours of the investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study drug must notify the investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, 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 or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium,

or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, 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.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints and Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that 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 CCI [redacted] (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.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate eCRF. Individuals

who identify a potential medication error situation should immediately report this via the phone number or email address provided below.

For Product Complaints or Medication Errors (Including Overdose) for MLN9708

CCI [redacted]

Product complaints or medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, an SAE form should be completed and sent to CCI [redacted] (refer to Section 10.2).

11.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

11.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

12. USE OF INFORMATION

All information regarding MLN9708 supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of MLN9708 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

13. INVESTIGATOR AGREEMENT

I have read Protocol C16014 Amendment 4: A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Newly Diagnosed Multiple Myeloma

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

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15. APPENDICES

15.1 Eastern Cooperative Oncology Group (ECOG) Scale for 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 al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.[80]

15.2 Multiple Myeloma Diagnostic Criteria

IMWG Criteria for the Diagnosis of Myeloma

Diagnosis	Diagnostic Criteria: All Three Required
Symptomatic multiple myeloma[a]	• Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma • Monoclonal protein present in the serum and/or urine[b] • Myeloma-related organ dysfunction (≥ 1)[c] [C] Calcium elevation in the blood (serum calcium > 10.5 mg/l or upper limit of normal) [R] Renal insufficiency (serum creatinine > 2 mg per 100 ml) [A] Anemia (hemoglobin < 10 g per 100 ml or 2 g <normal) [B] Lytic bone lesions or osteoporosis[d]

Source: International Myeloma Foundation, myeloma.org. Accessed 16 January 2012.

a These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma.

b If no monoclonal protein is detected (non-secretory disease), then ≥ 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

c A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

d If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then ≥ 30% plasma cells are required in the bone marrow.

15.3 Cockcroft-Gault Equation to Calculate the Creatinine Clearance

For males:

$$\text{Creatinine Clearance} = \frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[81]

15.4 ISS Staging Criteria and Durie-Salmon Criteria

International Staging System

Stage	Criteria
Stage I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
Stage II	Neither Stage I or Stage III[a]
Stage III	Serum β_2-microglobulin ≥ 5.5 mg/L

Source: Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36(3):842-54.[82]

Abbreviations: ISS = International Staging System.

a There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

Durie-Salmon Criteria

Stage	Criteria
I	All of the following: • Hemoglobin value > 10 g/dL • Serum calcium value normal or ≤ 12 mg/dL • Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only • Low M component production rate ○ IgG value < 5 g/dL; IgA value < 3 g/dL Bence Jones protein < 4 g/24 h
II	Neither stage I nor stage III

III	1 or more of the following:
	• Hemoglobin value < 8.5 g/dL
	• Serum calcium value > 12 mg/dL
	• Advanced lytic bone lesions (scale 3)
	• High M component production rate
	  ○ IgG value > 7 g/dL; IgA value > 5 g/dL
	  ○ Bence Jones protein >12 g/24 h

Durie-Salmon sub classifications (either A or B).

A: Relatively normal renal function (serum creatinine value < 2.0 mg/dL)

B: Abnormal renal function (serum creatinine value ≥ 2.0 mg/dL)

15.5 Steroid Equivalent Doses

Approximately equivalent doses:

Steroid	Glucocorticoid Anti-inflammatory (mg)	Mineralicorticoid (mg)	Half-life (hours)
Cortisone	100	100	8–12
Hydrocortisone	80	80	8–12
Prednisone	20	100	12–36
Prednisolone	20	100	12–36
Methylprednisolone	16	no effect	12–36
Dexamethasone	2	no effect	36–72

Source: Knoben JE, Anderson PO. Handbook of Clinical Drug Data, 6th ed. Drug Intelligence Pub, Inc. 1988.[83]

15.6 World Health Organization Steps of Analgesics and OME Conversions

15.6.1 Steps of Analgesics

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

WHO Step I
ACETAMINOPHEN & ASPIRIN
ACETAMINOPHEN & ASPIRIN & CAFFEINE
ACETAMINOPHEN & BUTALBITAL
ACETAMINOPHEN & BUTALBITAL & CAFFEINE
ACETAMINOPHEN & CAFFEINE
ACETAMINOPHEN CAP 500 MG
ACETAMINOPHEN CHEW TAB 80, 160 MG
ACETAMINOPHEN ELIXIR 80, 120 or 160 MG/5ML
ACETAMINOPHEN SOLN 100 MG/ML, 120 MG/2.5ML, 130 MG/5 ML, 160 MG/5ML
ACETAMINOPHEN SUPPOS 120 MG, 325 MG, 650 MG
ACETAMINOPHEN SUSP 80, 160 MG/5ML
ACETAMINOPHEN TAB 160, 325, 500, 650 MG
ACETAMINOPHEN TAB CR 650 MG
ACETAMINOPHEN W/ CALCIUM CARBONATE TAB 500-250 MG
ACETAMINOPHEN-BUTALBITAL CAP 650-50 MG
ACETAMINOPHEN-BUTALBITAL TAB 325-50 MG
ACETAMINOPHEN-BUTALBITAL TAB 650-50 MG
ACETAMINOPHEN-CAFFEINE-BUTALBITAL CAP 325-40-50 MG; 325-40-50 MG; 500-4-50 MG
ALUMINUM GLYCOLATE & ASPIRIN & MAGNESIUM CARBONATE
ALUMINUM HYDROXIDE & ASPIRIN & MAGNESIUM HYDROXIDE
ASPIRIN & BUTALBITAL & CAFFEINE
ASPIRIN & BUTALBITAL & CAFFEINE & PHENACETIN
ASPIRIN & CAFFEINE
ASPIRIN & CAFFEINE & PHENACETIN
ASPIRIN & PHENOBARBITAL
ASPIRIN BUFFERED (MG CARBONATE-AL GLYCINATE) TAB 325 MG
ASPIRIN BUFFERED (MG CARBONATE-AL GLYCINATE) TAB 500 MG
ASPIRIN BUFFERED TAB 325 MG; 500 MG
ASPIRIN CHEW TAB 75 MG
ASPIRIN EC TAB 81; 165; 325; 500;650;975 MG
ASPIRIN TAB 325; 500; 650 MG
ASPIRIN TAB CR 800 MG
ASPIRIN-ACETAMINOPHEN TAB 325-325 MG
ASPIRIN-ACETAMINOPHEN-CAFFEINE POWDER 260-130-16 MG

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

ASPIRIN-ACETAMINOPHEN-CAFFEINE TAB 230-125-30 MG;240-125-32 MG

ASPIRIN-ACETAMINOPHEN-CAFFEINE TAB 250-250-65 MG

ASPIRIN-AL HYDRO-MG HYDRO-CA CARB TAB 325-50-50-87 MG; 325-75-75-71 MG; 500-80-80-71 MG

ASPIRIN-AL HYDROXIDE-MG HYDROXIDE TAB 325-150-150 MG

ASPIRIN-AL HYDROXIDE-MG HYDROXIDE TAB 325-75-75 MG

ASPIRIN-APAP-CAFFEINE-CALCIUM GLUCONATE TAB 230-160-33-60 MG

ASPIRIN-BUTALBITAL TAB 650-50 MG

ASPIRIN-CAFFEINE TAB 400-30 MG; 500-30 MG

ASPIRIN-CAFFEINE-BUTALBITAL CAP 200-40-50 MG; 325-40-50 MG; 200-4-50 MG; 325-40-50 MG

ASPIRIN-CAL CARB-MAG OXIDE TAB 325-158-34-63 MG

ASPIRIN & PHENYLTOLOXAMINE CITRATE & SALSALATE

ASPIRIN EFFER TAB 325, 500 MG

ASPIRIN GUM 210 MG

ASPIRIN SUPPOS 125; 325; 650 MG

APC TAB 260-130-15 MG

BENOXAPROFEN

CHOLINE & MAGNESIUM SALICYLATES LIQ 500 MG/5ML

CHOLINE & MAGNESIUM SALICYLATES TAB 500, 750, 1000 MG

CHOLINE MAGNESIUM TRISALICYLATE

CHOLINE SALICYLATE

CINNAMEDRINE

DICLOFENAC POTASSIUM TAB 50 MG

DICLOFENAC SODIUM EC TAB 25, 50, 75 MG

DIFLUNISAL TAB 250, 500 MG

DIHYDROXYALUMINUM AMINOACETATE

ETHOHEPTAZINE CITRATE

ETODOLAC CAP 200, 300, 400 MG

FENOPROFEN CALCIUM CAP 200, 300, 600 MG

FLURBIPROFEN TAB 50, 100 MG

IBUPROFEN CHEW TAB 100 MG

IBUPROFEN POWDER

IBUPROFEN SUSP 100 MG/5ML

IBUPROFEN SUSP 40 MG/ML

IBUPROFEN TAB 100,200,300,400,600,800 MG

INDOMETHACIN CAP 25,50, 75 MG

INDOMETHACIN SODIUM IV FOR SOLN 1 MG

INDOMETHACIN SUPPOS 50 MG

INDOMETHACIN SUSP 25 MG/5ML

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

KETOPROFEN CAP 12.5, 25, 50, 75 MG
KETOPROFEN CAP CR 100, 150,200 MG
KETOROLAC TROMETHAMINE IM INJ 15, 30 MG/ML
KETOROLAC TROMETHAMINE TAB 10 MG
MAGNESIUM SALICYLATE TAB 500, 545, 600 MG
MAGNESIUM TRISILICATE
MECLOFENAMATE SODIUM CAP 50, 100 MG
MEFENAMIC ACID CAP 250 MG
MEPROBAMATE
METHOTRIMEPRAZINE HYDROCHLORIDE
NABUMETONE TAB 500, 750 MG
NAPROXEN SODIUM TAB 220, 275,550 MG
NAPROXEN SUSP 125 MG/5ML
NAPROXEN TAB 250, 375,500 MG
OXYPHENBUTAZONE
OXAPROZIN TAB 600 MG
PAMABROM
PHENYLBUTAZONE
PHENYLTOLOXAMINE
PHENYLTOLOXAMINE CITRATE
PIROXICAM CAP 10, 20 MG
PYRILAMINE
PYRILAMINE MALEATE
SALICYLAMIDE
SALSALATE TAB 500, 750 MG
SODIUM SALICYLATE TAB 325, 650 MG
SODIUM THIOSALICYLATE
SODIUM THIOSALICYLATE INJ 50 MG/ML
SULINDAC TAB 150, 200 MG
SUPROFEN
TOLMETIN SODIUM TAB 200, 400, 600 MG
ZOMEPIRAC SODIUM
WHO Step II
ACETAMINOPHEN & BUTALBITAL & CAFFEINE & CODEINE PHOSPHATE
ACETAMINOPHEN & HYDROCODONE BITARTRATE
ACETAMINOPHEN & OXYCODONE HYDROCHLORIDE
ACETAMINOPHEN & PROPOXYPHENE HYDROCHLORIDE
ACETAMINOPHEN & PROPOXYPHENE NAPSYLATE

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

ACETAMINOPHEN W/ CODEINE CAP 300-30 MG
ACETAMINOPHEN W/ CODEINE ELIXIR 120-12 MG/5ML
ACETAMINOPHEN W/ CODEINE TAB 300-15 MG; 300-30 MG; 300-60 MG; 300-7.5 MG; 650-30 MG
ACETAMINOPHEN W/ HYDROCODONE CAP 500-5 MG
ACETAMINOPHEN W/ HYDROCODONE ELIXIR 167-2.5 MG/5ML; 120-2.5 MG/5ML
ACETAMINOPHEN W/ HYDROCODONE TAB 500-2.5 MG;500-5 MG; 500-7.5 MG; 650-10 MG; 650-7.5 MG; 750-7.5 MG
ACETAMINOPHEN-CAFF-BUTALBITAL W/ COD CAP 325-40-50-30 MG
ACETAMINOPHEN-CAFFEINE-DIHYDROCODEINE CAP 356.4-30-16 MG
AL. HYDROXIDE & ASPIRIN & CODEINE PHOSPHATE & MG. HYDROXIDE
ASPIRIN & BUTALBITAL & CAFFEINE & CODEINE
ASPIRIN & BUTA & CAFF & CODEINE PHOSPHATE & PHENACETIN
ASPIRIN & CAFFEINE & CODEINE PHOSPHATE & PHENACETIN
ASPIRIN & CAFFEINE & HYDROCODONE BITARTRATE
ASPIRIN & CAFFEINE & PHENACETIN & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & CAFFEINE & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & CODEINE PHOSPHATE
ASPIRIN & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & PROPOXYPHENE NAPSYLATE
ASPIRIN W/ CODEINE TAB 325-15 MG; 325-30 MG; 325-60 MG
ASPIRIN W/ HYDROCODONE TAB 500-5 MG
ASPIRIN-CAFF-BUTALBITAL W/ CODEINE CAP 325-40-50-30 MG
ATROPINE SULFATE & MEPERIDINE HYDROCHLORIDE
ATROPINE SULFATE & MORPHINE SULFATE
BUPRENORPHINE HCL INJ 0.324 MG/ML
BUPRENORPHINE HYDROCHLORIDE
BUTORPHANOL TARTRATE INJ 1 MG/ML; 2 MG/ML
BUTORPHANOL TARTRATE NASAL SOLN 10 MG/ML
DEZOCINE INJ 10, 15 MG/ML
DIHYDROCODEINE COMPOUND CAP
MEPERIDINE W/ APAP TAB 50-300 MG
MEPERIDINE W/ ATROPINE INJ 50-0.4 MG/ML; 75-0.4 MG/ML
NALBUPHINE HCL INJ 10, 20 MG/ML
NALOXONE
NALTREXONE HCL TAB 50 MG
OXYCODONE W/ ACETAMINOPHEN SOLN 5-500 MG/5ML
OXYCODONE W/ ACETAMINOPHEN 5-325; 5-500 MG
OXYCODONE W/ ASPIRIN TAB FULL/half STRENGTH
OXYCODONE TEREPHTHALATE

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

PENTAZOCINE LACTATE INJ 30 MG/ML
PENTAZOCINE W/ APAP TAB 25-650 MG;12.5-325 MG
PROMAZINE HCL
PROMETHAZINE HCL (CAP & INJ)
PROPOXYPHENE COMPOUND CAP 65 MG
PROPOXYPHENE HCL W/ APAP TAB 65-650 MG;100-650 MG; 50-325 MG
WHO Step III
ALFENTANIL INJ 500 MCG/ML
CODEINE PHOSPHATE INJ 30, 60 MG/ML
CODEINE PHOSPHATE SOLN 15 MG/5ML
CODEINE PHOSPHATE SOLUBLE TAB 30, 60 MG
CODEINE SULFATE
CODEINE SULFATE TAB 30, 60 MG
FENTANYL CITRATE INJ 0.05 MG/ML
FENTANYL CITRATE POWDER
FENTANYL TD SYS 25, 50, 75, 100 MCG/HR
HYDROCODONE BITARTRATE
HYDROMORPHONE HCL INJ 1,2,3,4, 10 MG/ML
HYDROMORPHONE HCL LIQD 1 MG/ML
HYDROMORPHONE HCL POWDER
HYDROMORPHONE HCL SUPPOS 3 MG
HYDROMORPHONE HCL TAB 2,3,4,8 MG
LEVOMETHADYL ACETATE HCL SOLN 10 MG/ML
LEVORPHANOL TARTRATE INJ 2 MG/ML
LEVORPHANOL TARTRATE TAB 2 MG
MEPERIDINE HCL INJ 25, 50, 75, 100 MG/ML
MEPERIDINE HCL SYRUP 50 MG/5ML
MEPERIDINE HCL TAB 50, 100 MG
METHADONE HCL CONC 10 MG/ML
METHADONE HCL SOLN 5, 10 MG/5ML
METHADONE HCL TAB 5, 10, 40 MG
METHADONE HYDROCHLORIDE
MORPHINE SULFATE CAP 15, 30 MG
MORPHINE SULFATE IN DEXTROSE INJ 0.2 MG/ML
MORPHINE SULFATE IN DEXTROSE INJ 1 MG/ML
MORPHINE SULFATE INJ 1,2,3,4,5,8, 10,15,25,50 MG/ML
MORPHINE SULFATE INJ PF 0.5, 1 MG/ML
MORPHINE SULFATE ORAL SOLN 10, 20 MG/5ML; 20 MG/ML

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

MORPHINE SULFATE SUPPOS 5, 10, 20, 30 MG
MORPHINE SULFATE TAB 10, 15, 30 MG
MORPHINE SULFATE TAB CR 15, 20,60,100,200 MG
OXYCODONE HCL CONC 20 MG/ML
OXYCODONE HCL SOLN 5 MG/5ML
OXYCODONE HCL TAB 5 MG
OXYCODONE HYDROCHLORIDE
OXYMORPHONE HCL INJ 1 MG/ML
OXYMORPHONE HCL SUPPOS 5 MG
OXYMORPHONE HYDROCHLORIDE
PROPOXYPHENE HCL CAP 65 MG
PROPOXYPHENE NAPSYLATE SUSP 50 MG/5ML
PROPOXYPHENE NAPSYLATE TAB 100 MG
SUFENTANIL CITRATE INJ 50 MCG/ML
TRAMADOL HCL TAB 50 MG

Source: World Health Organization. Cancer Pain Relief. Geneva: World Health Organization, 1986.[84]

15.6.2 Oral Morphine Equivalent (OME) Conversions

Table 15-2 Oral and Parenteral Opioid Equivalences and Relative Potency of Drugs as Compared With Morphine

Opioid Agonists[a]	Oral Dose (mg)	Parenteral Dose (mg)	Factor (IV to PO)
Morphine[b]	***30***[b]	10	3
Codeine	200	130	1.5
Fentanyl[c]		0.1 (100 µg)	
Hydrocodone	30 to 200		
Hydromorphone	7.5	1.5	5
Levorphanol	4	2	2
Oxycodone	15 to 20		
Oxymorphone	10	1	10
Tramadol[d]	50 to 100		

Source: Adapted from the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, Adult Cancer Pain, V.1.2010.[85]

a Opioid drugs NOT recommended include meperidine, methadone, propoxyphene, partial agonists (buprenorphine), and mixed agonist-antagonists (pentazocine, nalbuphine, butorphanol, dezocine).

b Oral morphine equivalent (OME) score is based on an oral morphine dose of 30 mg; the conversion factor listed is for chronic dosing. Avoid using morphine in renal failure.

c Available in transdermal system for extended dosing. See the calculation below for dose conversion from other opioids to transdermal fentanyl.

d Weak opioid receptor agonist with some antidepressant activity; for mild to moderate pain. Recommended dose of 100 mg 4 times daily (maximum daily dose of 400 mg) to avoid central nervous system toxicity. At maximum dose, tramadol is less potent than other opioid analgesics.

Oral Morphine Equivalence Conversion Calculation

To calculate the OME score of an opioid in Table 15-2:

X = dose of an opioid equivalent to an oral morphine dose of 30 mg

Y = dose of that opioid consumed by the patient in the last 24 hours

OME of that opioid consumed in the last 24 hours = Y / X × 30

Example: A patient consumed 100 mg of oral codeine in the last 24 hours. The OME calculation is:

X = 200 mg

Y = 100 mg

OME of oral codeine = 100 / 200 × 30 = 15 mg

Table 15-3 Recommended Dose Conversion From Other Opioids to Transdermal Fentanyl

Transdermal Fentanyl (µg/d)	*Morphine*		Oxycodone		Hydromorphone		Codeine	
	Oral[a] (mg/d)	IV/SubQ[b] (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)
25	***60***	20	30	15	7.5	1.5	200	130
50	120	40	60	30	15	3.0	400	260
75	180	60	90	45	22.5	4.5	600	390
100	240	80	120	60	30.0	6.0	800	520

Source: Adapted from the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, Adult Cancer Pain, V.1.2010.[85]

Due to patient variability the recommended doses are estimates; clinical judgment should be used to titrate to the desired response.

a Oral morphine equivalent (OME) score is based on an oral morphine dose of 60 mg (as adapted from Foley KM. The treatment of cancer pain. NEJM 1985; 313:84-95 [86]).

b Parenteral dosing such as intravenous or subcutaneous.

15.7 EQ-5D

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

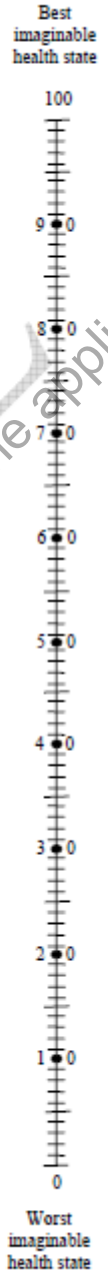
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

 2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



15.8 Brief Pain Inventory-Short Form (BPI-SF)

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

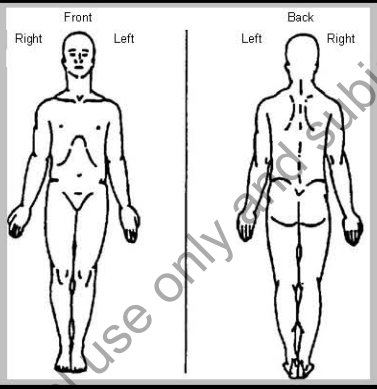
Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:___/____/____ Time:_____
Name:_____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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15.9 QLQ-MY20

EORTC Multiple Myeloma Module (QLQ-MY20)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

15.10 European Organization for Research and Treatment of Cancer (EORTC QLQ-C30 (Version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): |_|_|_|_|_|_|_|_|_|_|

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

15.11 Response Criteria [72]

Patients will be assessed for disease response according to the IMWG criteria below, version 2011.

Table 1. IMWG uniform response criteria by response subcategory for multiple myeloma[7]

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	Not meeting criteria for CR, VGPR, PR, or PD	Increase of 25% from lowest response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio *and*	≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria		Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or*
< 5% PCs in bone marrow	Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry		If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30%		Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or*
			In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required		Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
					Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)
					Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
					Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

Adapted from Durie et al[7] and Kyle et al[13] with permission. All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

PCs indicate plasma cells.

*Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

†Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

For VGPR: Disappearance of any soft tissue plasmacytomas present at baseline and no new plasmacytomas.

International Myeloma Working Group Uniform Response Criteria: Disease Progression and Relapse [72]

Relapse Subcategory	Relapse Criteria
PD[a] To be used for calculation of time to progression and PFS endpoints for all subjects, including those in CR (includes primary progressive disease and disease progression on or off therapy)	PD: requires any 1 or more of the following: Increase of ≥ 25% from nadir in Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[b] Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Bone marrow plasma cell percentage: the absolute % must be ≥ 10% Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.85 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Abbreviations: CR = complete response; PFS= progression-free survival.

a All relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.

b For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

15.12 Amendment 1 Rationale and Purposes

Rationale for Amendment 1

The primary rationale for this amendment is to add a study objective evaluating progression-free survival 2 (PFS2), defined as the date from randomization to the date of second disease progression or death from any cause, whichever comes first. Procedures and assessments required for evaluation of PFS2 have been added throughout the protocol.

In addition, a second assessment of MRD was added for patients who have an initial confirmed complete response.

Directions for administration of lenalidomide and dexamethasone were clarified to align more closely with the package insert and the SmPC.

Instructions for dose modifications were additionally clarified based on the evolving understanding of MLN9708 and its overlapping toxicities with lenalidomide and dexamethasone. In addition, Section 6.10, Management of Clinical Events, has been updated to reflect the most recent understood safety profile of MLN9708.

Language was added in case of unblinding to clarify that sites must provide justification of unblinding and receive approval from the sponsor before unblinding.

Other changes clarify study procedures, as noted in the following list.

Purposes for Amendment 1

The purposes of this amendment are to:

- Add the Intergroupe Francophone du Myelome number
- Update the cover page with current signatories
- Update the study overview diagram to remove subsequent antineoplastic therapy as a grounds for treatment discontinuation, add PFS2, and clarify flow of patients depending on disease response
- Clarify permissible window for obtaining informed consent
- Permit local laboratory evaluation of Cycles 1 and 2, Days 7 and 21 complete blood count assessments
- Clarify timing of radiographic disease assessment
- Clarify timing for serum protein electrophoresis, urine protein electrophoresis, serum free light chain assay, and immunofixation
- Clarify timing of bone marrow aspirate for molecular analysis and cytogenetics
- Clarify timing of bone marrow aspirate for MRD
- Clarify required documentation of peripheral neuropathy
- Add collection of subsequent therapy and disease status for assessment of PFS2
- Add the duration of time permitted between randomization and initiation of treatment with the study drug regimen
- Clarify the pharmacokinetic sampling schedule
- Clarify the definition of the overall survival follow-up period

- Clarify the description of MLN9708
- Update the details of the MLN9708 potential risks and benefits
- Clarify doses of the study drug and lenalidomide beyond 18 cycles of treatment
- Clarify that the assessment of disease response/progression is done by both the independent review committee and investigator during the treatment period and PFS follow-up period, and only by the investigator during the overall survival follow-up period for determination of PFS2
- Update the list of participating sites
- Clarify permitted creatinine clearance values for reduced lenalidomide dosing
- Updated the name of Revlimid RevAssist® to Revlimid REMS™ and specify that counseling must be documented
- Clarify the details for concurrent aspirin use
- Clarify the eligibility criteria regarding prior radiotherapy
- Update exclusion criteria regarding prior diagnosis of or therapy for malignancy
- Clarify the exclusion criteria regarding thromboembolism prophylaxis
- Clarify eligibility for patients with cardiovascular disorders
- Update exclusion criteria regarding infection
- Clarify the exclusion criteria regarding prior treatment with an investigational product
- Clarify confirmation and documentation of eligibility before randomization
- Clarify and standardize study drug and study drug regimen terminology
- Clarify lenalidomide administration guidelines
- Clarify dexamethasone administration guidelines
- Clarify dose modification guidelines
- Clarify within cycle versus before beginning next cycle dose modifications
- Clarify dose adjustment procedures for rash
- Clarify study drug treatment modifications
- Clarify lenalidomide treatment modification guidelines
- Clarify dexamethasone dose modification guidelines
- Clarify criteria for toxicity recovery before beginning the next cycle of treatment
- Clarify prohibited procedures
- Clarify permitted concomitant medications and procedures
- Add digoxin to the list of precautions and restrictions
- Update language describing the management of clinical events
- Indicate that protocol changes will be communicated to the investigative sites at the time the study is unblinded
- Clarify the description of the preparation, reconstitution, and dispensation of MLN9708 to be consistent across studies

- Clarify the description of the storage and handling of MLN9708 to be consistent across studies
- Clarify shifts in study procedures for holidays, vacation, and other administrative reasons
- Clarify assessments to be collected as part of medical history
- Clarify the roles of the central and local laboratories for eligibility, progressive disease assessment, and safety
- Clarify the timing of skeletal surveys
- Clarify the timing of dual-energy X-ray absorptiometry scans
- Clarify timing of M-protein assessments
- Clarify central vs local laboratory bone marrow evaluations
- Add in the response assessment version and clarify the timing assessment of disease response
- Clarify the M-protein and free light chain to be followed for response assessment according to International Myeloma Working Group criteria
- Clarify the specific bone metabolism biomarkers to be measured, as well as the sampling schedule and conditions
- Add assessment of PFS2
- Add a treatment discontinuation form to ensure review and approval of progressive disease before removing patient from treatment
- Clarify assessment of pain
- Clarify biomarker analysis is to be done for disease response, not only complete response
- Remove the Steering Committee
- Add that the independent data monitoring committee will receive reports of all cases of new primary malignancies during the study
- Indicate proper reporting of overdose
- Update the SAE reporting contact information
- Update procedures for SAE reporting
- Clarify instructions about how and when to report and manage pregnancies
- Correct typographical errors, punctuation, grammar, and formatting

15.13 Amendment 1A Rationale and Purposes

Rationale for Amendment 1A

The primary rationale for this amendment is to establish a continuation of Study C16014 in South Korea to enroll additional patients from South Korea only. This amendment describes modifications to the global study procedures specifically for patients who enroll in the South Korea continuation. Patients from South Korea who enroll in the global C16014 study will not be affected. Following completion of enrollment in the global study (701 patients), approximately 40 additional patients from South Korea will be enrolled in the continuation.

The South Korea continuation is an extension of the global study that will continue to assess the primary objective of progression-free survival (PFS) and secondary objectives of complete response rate, overall survival (OS), and pain response rate in patients from South Korea. Other secondary objectives that directly relate to disease response assessment, safety, and patient-reported outcomes will also be evaluated to thoroughly characterize the efficacy and safety of MLN9708 in combination with lenalidomide and dexamethasone. Some secondary and exploratory objectives will be explored in the global study but are not included in the South Korea continuation because they are signal-seeking in nature and require a larger number of patients to detect a difference between arms.

The statistical and quantitative analyses, including timing of the PFS and OS analyses, have been revised to reflect the change in sample size. The primary objective of PFS will be assessed when approximately 40 PFS events have been reported in patients from South Korea (pooled from patients enrolled in the global study and the continuation). OS will be assessed at the time of the final analysis of OS in the global study or when a total of 40 death events have been reported for patients in South Korea (pooled between global study patients and South Korea continuation patients), whichever occurs later, or termination of the study by the sponsor.

Purposes for Amendment 1A

The purposes of this amendment are to:

- Update signatories to reflect clinicians involved in this protocol
- Update the number of patients from 701 to 40 to reflect the approximate number of patients from South Korea that will be enrolled in the continuation
- Reclassify key secondary objectives and other secondary objectives as 1 category of secondary objectives
- Remove secondary objectives (and corresponding endpoints and study procedures) that do not directly contribute to the characterization of the efficacy or safety of MLN9708
- Remove exploratory objectives (and corresponding endpoints and study procedures) that do not directly contribute to the characterization of the efficacy or safety of MLN9708
- Clarify lenalidomide dose modification language for patients with low creatinine clearance to align with the South Korean label
- Modify the time and number of events required for analysis of PFS

- Modify the time and number of events required for analysis of OS
- Modify the statistical procedures for secondary efficacy
- Specify that the study population is comprised of patients from South Korea
- Modify the duration of study for patients in the continuation
- Revise global text for pregnancy testing to only state instruction for South Korea
- Revise global text for supply of lenalidomide to only state instruction for South Korea
- Clarify the patient-reported outcomes analysis
- Clarify the time to pain progression and duration of pain response analyses
- Correct typographical errors, punctuation, grammar, and formatting

15.14 Amendment 2 Rationale and Purposes

Rationale for Amendment 2

The primary rationale for this amendment is to modify the statistical analysis plan to prevent early closure of the study in the light of the importance of collecting long-term patient outcomes data.[86] To do so, an additional IA has been added later in the study, while maintaining the previous first IA for progression-free survival (PFS) at approximately 326 events. The new second IA will analyze PFS at approximately 435 events only if the threshold for significance was not met at the first IA; otherwise, the first IA will serve as the final PFS analysis for the study, and the second IA will be conducted to assess overall survival (OS) when approximately 250 deaths have occurred. The addition of this second IA will safeguard the PFS statistical power at 95%, and serve to determine whether the final number of OS events might be increased from approximately 320 death events to up to approximately 400 death events using unblinded event re-estimation by an ISC.

In addition, this amendment modifies the study assessments to be performed after PFS significance is met. Endpoints relating to disease response (ie, PFS, response rate, time-to-progression) will not be assessed for protocol purposes after the primary endpoint is met; as such, all efficacy response data (ie, laboratory samples) will stop being collected/sent to the central laboratory to minimize the burden on study patients.

Other changes clarify study procedures, as noted in the following list.

Purposes for Amendment 2

The purposes of this amendment are to:

- Update the title page with current signatories
- Change the order of the key secondary objectives to move the complete response (CR) objective to appear after the overall survival (OS) objective
- Reclassify the objective regarding evaluation of the relationship between polymorphisms in the proteasome and NFKB-related genes and response from secondary to exploratory
- Clarify the definition of skeletal-related events
- Add a second IA to assess PFS (only if significance is not reached at the first IA) and OS
- Discontinue efficacy response assessments for protocol purposes after PFS significance has been met in the study (either at the first IA or second IA), except for investigator assessment of PFS2 (progression-free survival 2 [from randomization on study to PFS on the next line of treatment])
- Remove reference to the Safety Management Attachment
- Remove Ginkgo biloba as an excluded medicinal product
- Clarify shifts in study procedures for holidays, vacations, and other administrative reasons
- Clarify the procedure for assessment of PFS2

- Update the pharmacokinetics (PK) and concomitant medication information to reflect recent population PK analyses and drug-drug interaction study results from Study C16009 demonstrating that cytochrome P450 inhibitors do not affect MLN9708 PK
- Clarify the definition of the End of Treatment visit
- Clarify the administration instructions for MLN9708
- Clarify the management of rash
- Clarify the management of overdose
- Clarify the instructions for study drug dispensing
- Clarify the storage conditions for MLN9708
- Clarify the procedure for performing the physical examination
- Clarify the timing of bone marrow aspirates for minimal residual disease
- Clarify when central laboratory results must be reviewed before initiating the next treatment cycle
- Add an email address for reporting adverse events and serious adverse events in Japan
- Clarify the monitoring of adverse events and period of observation
- Update the procedures for product complaints to include instructions for reporting medication errors and overdose
- Correct typographical errors, punctuation, grammar, and formatting

15.15 Amendment 2A Rationale and Purposes

Rationale for Amendment 2A

This amendment describes modifications that were made to the C16014 global study procedures (Global Amendment 2) that apply to the Korea-specific protocol continuation.

Purposes for Amendment 2A

The purposes of this amendment are to:

- Update the title page with current signatories
- Update the pharmacokinetics (PK) and concomitant medication information to reflect recent population PK analyses and drug-drug interaction study results from Study C16009 demonstrating that cytochrome P450 inhibitors do not affect MLN9708 PK
- Clarify when bone marrow aspirate will be collected for assessment
- Remove reference to the Safety Management Attachment
- Clarify the timing of bone marrow aspirates for minimal residual disease
- Change the order of the secondary objectives to move the CR objective to appear after the OS objective
- Clarify the timing of flow cytometry
- Clarify the definition of skeletal-related fractures to be evaluated
- Clarify the recommended frequency for response assessments
- Clarify the definition of the End of Treatment visit
- Clarify the administration instructions for MLN9708
- Provide reference to updated excluded concomitant medication
- Remove Ginkgo biloba as an excluded medicinal product
- Clarify the management of rash
- Clarify the management of overdose
- Clarify storage conditions of MLN9708 and also clarify shifts in study procedures for holidays, vacations, and other administrative reasons
- Provide reference for storage and shipping guidelines
- Clarify the procedure for assessment of progression-free survival 2 (PFS2) and shifts in study procedures for holidays, vacations, and other administrative reasons
- Clarify the procedure for performing the physical examination
- Clarify when central laboratory results must be reviewed before initiating the next treatment cycle
- Delete sensitivity analyses for CR rate
- Clarify analgesic use
- Overdose deleted from list of medically important event
- Update serious adverse event (SAE) Reporting Contact Information

- Clarify the monitoring of AEs and period of observation
- Update the procedures for product complaints to include instructions for reporting medication errors and overdose
- Section of new text added to comply with ICH E6 (GCP) regulations regarding investigator responsibilities
- Correct typographical errors, punctuation, grammar, and formatting

15.16 Amendment 3 Rationale and Purposes

Rationale for Amendment 3

This document describes the changes in reference to the protocol incorporating Amendment No. 3. The primary reason for this amendment is to follow the independent data monitoring committee (IDMC) recommendation to include a subgroup analysis approach focusing on patients who could derive particular benefit from ixazomib with manageable toxicity. To do so, a progression-free survival (PFS) subgroup analysis testing strategy approach is prospectively included to be executed at the second interim analysis in parallel with the PFS analysis in the intent-to-treat (ITT) population should the first interim analysis fail to demonstrate a statistically significant PFS advantage in the ITT population. The addition of this analysis will serve to determine whether the ixazomib treatment arm shows superiority over the placebo control arm on the primary endpoint of PFS in 3 prespecified subgroups using the Hochberg procedure for multiplicity correction: 1) patients with baseline creatinine clearance > 60 mL/min, 2) patients < 75 years of age, and 3) patients harboring high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), amp(1q21).

Minor grammatical, editorial, formatting, and administrative changes are included for clarification purposes only. For specific examples of changes in text and where the changes are located, see Section 15.17.

Changes in Amendment 3

1. Update the statistical procedures to reflect a prespecified subgroup testing strategy.

15.17 Amendment 4 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Amendment No. 4 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Clarify the exploratory endpoints to reflect current understanding of the association between response/resistance and patient outcomes in key signaling pathways.

The primary change occurs in Section 3.3 Exploratory Endpoints and Section 1.6.3 Rationale for the Molecular Analyses:

Added text: Section 3.3:

…

- Association between response/ resistance and patient outcome to MLN9708 treatment and mutations in key pathways, such as **NFKB and** RAS/RAF, or any key signaling pathways determined to be clinically meaningful
- Association between response/ resistance and patient outcome to MLN9708 treatment and tumor gene expression patterns including **TRAF3,** NFKB**,** and protein synthesis signatures, as well as pathways activity and transcripts levels determined to be clinically meaningful

…

Added text: Section 1.6.3 Rationale for the Molecular Analyses

The heterogeneity of clinical results with myeloma therapeutics is partly related to variation in the molecular subtypes of myeloma and the complex interaction of each tumor with the biology of the host. Several clinical studies have shown that tumor biology can be directly related to the clinical efficacy of either multidrug combinations in myeloma (a validated gene expression model of high-risk MM is defined by deregulated expression of genes mapping to chromosome 1 [39-41] or to outcome after single-agent VELCADE therapy).[42,43] These studies highlight links between TRAF3, a key regulator of the NFKB pathway, and protein synthesis with clinical sensitivity and resistance respectively to VELCADE. A recent whole genome sequencing study of MM patients reported the presence of mutations in known cancer genes that had either not previously been reported in MM such as human homolog of a murine sarcoma viral oncogene (BRAF), or that were present at much higher frequency in MM than previously reported (KRAS, NRAS).[44] Similar studies with samples from VELCADE clinical trials highlighted the link between mutations in these pathways and response to proteasome inhibitor.[45] **A link between the NFKB pathway activity and clinical sensitivity to MLN9708 plus lenalidomide and dexamethasone in patients with relapsed and/or refractory multiple myeloma (RRMM) was also seen in the C16010 study. In this study, increased clinical benefit was observed in patients whose tumors harbored mutations in the non-canonical NFKB pathway or who had decreased**

expression of TRAF3.[46]
In this clinical study, a screening tumor sample will be collected from each patient to test the link between clinical outcomes and the presence of specific gene mutations in the **NFKB and** RAF/RAS pathway, expression of **TNF receptor-associated factor 3 (TRAF-3),** NFKB**,** and protein synthesis gene signatures, or WNT/β-catenin pathway activation. These hypotheses will be tested in all patients. Additional analyses of tumor molecular characteristics may be done to identify biomarkers determined to be clinically meaningful in this study. These tumor analyses may include but are not limited to gene expression, deoxyribonucleic acid (DNA) mutations, and/or epigenetic factors. These analyses will also be done in tumor samples collected from patients who initially respond to therapy and subsequently relapse.
…

Rationale for Change: To reflect current understanding of the association between response/resistance and patient outcomes in key signaling pathways.

The following sections also contain this change:

- Protocol Summary
- Section 2.3 Exploratory Objectives
- Section 8.1.8.2 Biomarker Analysis

Change 2: Update statistical procedures to modify the number of events for the final PFS analysis.

The primary change occurs in Section 8.1.1 Determination of Sample Size.

Initial text: …

Assuming a hazard ratio of 0.70 (median PFS of 25 months in control arm versus 35.8 months in treatment arm), 435 PFS events will be needed (95% power and 2-sided alpha of 0.05) with up to 2 planned PFS analyses conducted at the first IA and potentially second IA of this study using the Gamma(-1) alpha spending function.

The first IA will be performed when approximately 326 PFS events have occurred. This is expected to occur approximately 45 months after the first patient is enrolled, including a 27-month enrollment period and additional 18-month follow-up from the last patient.

If the test for PFS in the ITT population is statistically significant at the first IA, this will be the FA for PFS for statistical testing purposes, and the second IA will assess OS when approximately 250 death events have occurred.

If the test for PFS in the ITT is not statistically significant at the first IA, then the second IA will assess PFS and OS when approximately 435 PFS events have occurred. In addition, in such a case, PFS will be tested at IA2 in 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21).

…

Amended or new text:

…

Assuming a hazard ratio of 0.70 (median PFS of 25 months in control arm versus 35.8 months in treatment arm), ~~435~~**370** PFS events will be needed (~~95~~**92**% power and 2-sided alpha of 0.~~05~~**04**) with up to 2 planned PFS analyses conducted at the first IA and potentially second IA of this study using the Gamma(-1) alpha-spending function.

The first IA will be performed when approximately 326 PFS events have occurred. This is expected to occur approximately 45 months after the first patient is enrolled, including a 27-month enrollment period and additional 18-month follow-up from the last patient.

If the test for PFS in the ITT population is statistically significant at the first IA, this will be the FA for PFS for statistical testing purposes, and the second IA will assess OS when approximately 250 death events have occurred.

If the test for PFS in the ITT is not statistically significant at the first IA, then the second IA will assess PFS and OS when approximately ~~435~~**370** PFS events have occurred. In addition, in such a case, PFS will be tested at IA2 in 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21).

…

Rationale for Change: To update statistical analysis details.

The following sections also contain this change:

- Section 4.1 Overview of Study Design.
- Section 8.1.10 Interim Analysis.

Change 3: Clarify the statistical boundary for PFS at the second IA.

The primary change occurs in Section 8.1.10 Interim Analysis.

Added text: …

> **Because at the time of this amendment, the boundary for ITT PFS at IA1 has already been calculated based on 328 PFS events observed at IA1, 435 PFS events targeted at PFS final analysis, and the Gamma(-1) alpha-spending function, this boundary will not be changed. However, the boundary for ITT PFS at IA2 (final analysis of ITT PFS) will be calculated based on the observed number of PFS events at IA2 in order to spend what is left of the overall alpha-level 0.04 for ITT. The final boundaries at IA1 and IA2 will not approximate a Gamma(-1) function, but type I error will remain protected under the flexible alpha-spending approach (see appendix in the SAP for more details).**
>
> …

Rationale for Change: Clarify the updated PFS boundary.

Change 4: Clarify that REVLIMID or generic lenalidomide may be administered as part of the study treatment regimen.

The primary change occurs in Section 6.2.1 Lenalidomide Administration.

Added text: …

> **Upon implemention of this amendment, lenalidomide may be administered as commercial REVLIMID or as generic lenalidomide through clinical trial material.**

Rationale for Change: Clarify lenalidomide administration details.

The following sections also contain this change:

- Section 5.1 Inclusion Criteria.
- Section 6.9 Contraception Requirements.
- Section 6.15.1.1 Lenalidomide8.1.8.2.

Change 5: Remove the requirement to document adverse events that require breaking the blind in the eCRF.

The primary change occurs in Section 6.11 Blinding and Unblinding.

Deleted text:

…

Records of the patient number, the date each drug in the study drug regimen was dispensed, and the treatment assignment will be maintained by the study site. If the treatment assignment must be revealed for the safety of the patient or to treat an AE, the investigator will contact the Millennium clinician/ study clinician designee. A decision to break the blind must be reached by the Millennium clinician/study clinician designee and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Millennium clinician/ study clinician designee if it is considered to be an emergency by the investigator that requires specific knowledge of the blinded study treatment in order to properly treat the AE/safety issue. If the treatment of the AE/ safety issue is the same regardless of the study drug assignment, the blind should not be broken. ~~The event requiring breaking the blind must be documented in the electronic case report form (eCRF), including the date the blind was broken.~~ In addition, the patient will be discontinued from further study drug administration in this study.

…

Rationale for Change: To correct details about documenting breaking of the blind.

Change 6: Update the SAE reporting contact information in Japan to CCI .

The primary change occurs in Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events.

Initial text: ···

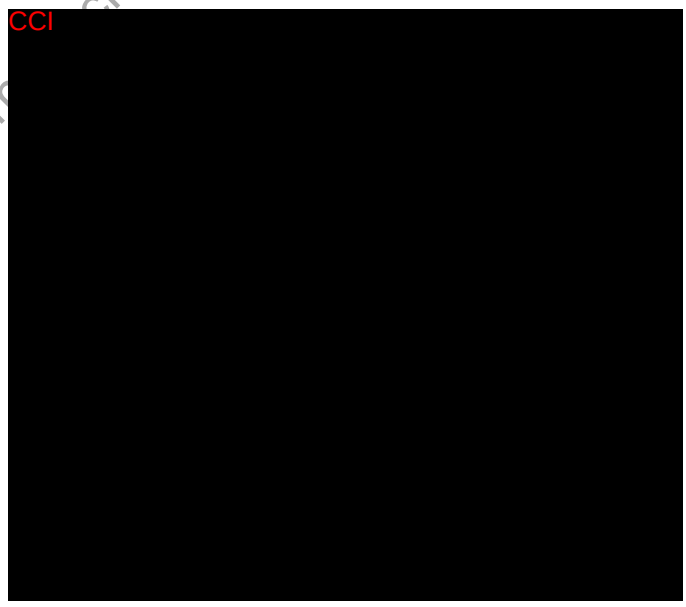
CCI

···

Amended or new text: ···

SAE Reporting Contact Information

CCI



···

Rationale for Change: To update SAE reporting information in Japan.

Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events also contains this change.

Change 7: Clarify the duration of new primary malignancy AE assessment.

The primary change occurs in Section 10.3 Monitoring of Adverse Events and Period of Observation.

Initial text: …

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRF. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). In addition, all cases of new primary malignancy that occur during the follow-up periods must be immediately reported to the Millennium Department of Pharmacovigilance or designee, irrespective of causality to the study drug regimen, from the first dose of the study drug regimen through death, until termination of the study by the sponsor, or for a minimum of 3 years after the last dose of the investigational product, whichever comes first. The IDMC will also receive reports of all cases of new primary malignancies occurring during the trial.

Amended or new text: …

Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRF. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). In addition, all cases of new primary malignancy that occur during the follow-up periods must be immediately reported to the Millennium Department of Pharmacovigilance or designee, irrespective of causality to the study drug regimen, from the first dose of the study drug regimen through death~~,~~ **or** until termination of the study by the

sponsor, ~~or for a minimum of 3 years after the last dose of the investigational product,~~ whichever comes first. The IDMC will also receive reports of all cases of new primary malignancies occurring during the trial.

Rationale for Change: To clarify details of new primary malignancy AE assessment.

Change 8: Clarify the locations of study centers.

The primary change occurs in Section 4.2 Number of Patients**.**

Initial text: Approximately 701 patients will be enrolled in this study from approximately 150 study centers in North America, Europe, Russia, and Australasia. Enrollment is defined as being randomized to treatment in the study.

Amended or new text: Approximately 701 patients will be enrolled in this study from approximately 150 study centers in North America, Europe, Russia, **New Zealand,** and ~~Australasia~~**Asia**. Enrollment is defined as being randomized to treatment in the study.

Rationale for Change: To update study center locations.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	10-Aug-2019 18:50 UTC
	Clinical Science Approval	10-Aug-2019 21:44 UTC
	Statistical Approval	12-Aug-2019 15:13 UTC

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Newly Diagnosed Multiple Myeloma

Protocol #: C16014

SAP History

Original	16 March 2018
Amendment 1	14 January 2020

Approved by:

Note: If this document was approved electronically, then the electronic approval signatures may be found at the end of the document.

PPD

_____
Date

_____
Date

_____
Date

_____
Date

Rationale for Amendment 1

This document describes the changes in reference to the statistical analysis plan (SAP) incorporating Amendment No. 1. The primary reason for this amendment is to modify the SAP to ensure timely analysis of the primary endpoint, progression-free survival (PFS), in light of the slower than expected PFS event rate over the past year. The second interim analysis (IA) – the final analysis for PFS – will now take place when approximately 370 PFS events have been observed. Power remains sufficient at 92%.

Minor grammatical, editorial, formatting, and administrative changes are included for clarification purposes only.

Changes in Amendment 1

1. Update statistical procedures to modify the number of events for the final PFS analysis.
2. Clarify the statistical boundary for PFS at the second IA.
3. CCI [redacted]
4. Update list of covariates in the adjustment of overall survival analysis for potential confounding effects by subsequent therapies after patients discontinue study treatment.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASCT	autologous stem cell transplant
BM	bone marrow
BSA	body surface area
CBC	complete blood count
CFR	Code of Federal Regulations
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	coefficient of variation
CYP	cytochrome P_{450}
DDI	drug-drug interaction(s)
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
EOT	End of Treatment (visit)

Abbreviation	Term
EU	European Union
FA	final analysis
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	hemoglobin
CC[redacted]	[redacted]
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
CCI[redacted]	[redacted]
IMWG	International Myeloma Working Group
IRB	institutional review board
IRC	independent review committee
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
KPS	Karnofsky Performance Status
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Term
NDMM	Newly diagnosed multiple myeloma
CCI	[redacted]
ORR	overall response rate
OS	Overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease (disease progression)
PFS	Progression-free survival
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial remission ***or*** partial response
PRO	patient-reported outcome(s)
PSA	prostate-specific antigen
CCI	[redacted]
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	subcutaneous
SCT	stem cell transplant
SD	stable disease
SMA	Safety Management Attachment to the Investigator's Brochure
$t_{1/2}$	terminal disposition half-life
TEAE	Treatment-emergent adverse event
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
CCI	[redacted]
TTP	Time to (disease) progression
ULN	upper limit of the normal range
US	United States
VGPR	Very good partial response
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

In general, the purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This is a phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of MLN9708 versus placebo when added to lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma (NDMM). Patients must be previously untreated for symptomatic MM, be ineligible for high-dose therapy plus stem cell transplantation (HDT-SCT) because of age (ie, ≥ 65 years) or coexisting conditions per investigator judgment, be candidates for treatment with lenalidomide and dexamethasone as their standard therapy, and meet other eligibility criteria.

Following the Screening period, patients to be enrolled will be randomized to receive either MLN9708 or placebo in a double-blind fashion in addition to the background therapy of lenalidomide plus dexamethasone (LenDex). Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms, stratified by age (<75 years vs ≥75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs ≥4) at Screening.

Patients may continue to receive treatment for a maximum duration of 18 cycles (approximately 18 months with 28 days per cycle), or until progressive disease (PD) or unacceptable toxicity, whichever comes first. Patients remaining on study after 18 cycles will continue treatment in the same randomization arm on the same schedule with modified dose levels of the study drug and LenDex: reduce MLN9708 (or placebo) dose to 3.0 mg, reduce lenalidomide dose to 10 mg, and no dexamethasone.

Patients will be assessed for disease response and progression by an independent review committee (IRC). Response will be assessed according to the International Myeloma Working Group (IMWG) criteria for all patients every cycle during the treatment period and subsequently every 4 weeks during the PFS follow-up period until disease progression. All patients will be followed for survival after progression. Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

1.2 Study Objectives

The primary objective is:

- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves progression-free survival (PFS) in patients with NDMM

The key secondary objectives are:

- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves overall survival (OS)
- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves the rate of complete response (CR)
- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves pain response rate, as assessed by the Brief Pain Inventory – Short Form (BPI-SF) and analgesic use

Other secondary objectives are:

- To determine overall response rate (ORR), including partial response (PR), very good partial response (VGPR), and CR
- To determine time to response (TTR), duration of response (DOR), and time to progression (TTP)
- To determine the effect of the addition of MLN9708 to lenalidomide and dexamethasone on progression-free survival 2 (PFS2), defined as the date from randomization to the date of second disease progression or death from any cause, whichever comes first
- To determine the safety of the addition of MLN9708 to lenalidomide and dexamethasone
- To assess change in global health status, as measured by the global health status, functioning, and symptoms as measured by the patient-reported outcome (PRO) instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and MY20 module

- To determine the PFS and OS in high-risk cytogenetic patient groups defined by the following cytogenetic abnormalities: t(4;14), t(14;16), amp(1q21), and del(17p)

- To evaluate minimal residual disease status (MRD), via flow cytometry, in patients suspected to have reached CR at any time during the entire conduct of the study, and at Cycle 18 for patients who have maintained a CR until that point. The impact of MRD status on TTP, PFS, and OS will be assessed.

- To assess time to pain progression

- To collect pharmacokinetic (PK) data to contribute to population PK analyses

- To evaluate the frequency of skeletal-related events (eg, new fractures [including vertebral compression or rib fractures], irradiation of or surgery on bone, or spinal cord compression) from baseline through the last survival assessment

Exploratory Objectives are:

CCI

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[redacted]

2. POPULATIONS FOR ANALYSIS

2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all patients who are randomized. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing. If patients are regarded as screen failure, either were not randomized yet, or were randomized without being dosed, they will be excluded from ITT population.

The ITT population will be used for the primary, secondary efficacy analyses, and resource utilization and patient reported outcome analysis.

2.2 Safety Population

The safety population is defined as all patients who receive at least 1 dose of any study drug. Patients will be analyzed according to the treatment actually received. That is, those patients who are randomized to the active arm but receive the regimen in the control arm will be included in the control arm; those patients who are randomized to the control arm but receive the regimen in the active arm will be included in the active arm for safety analyses. More specifically, patients who received any dose of ixazomib will be included in the MLN9708 + LenDex arm and patients who did not receive any dose of ixazomib will be included in the placebo plus LenDex arm, regardless of their randomized treatment.

Safety population will be used for all safety related analyses such as AE, concomitant medication, laboratory tests, and vital signs.

2.3 Response-Evaluable Population:

The response-evaluable population was defined as all patients in the ITT population who receive at least 1 dose of any study drug, have measurable disease at baseline, and at least 1 post baseline response assessment assessed by an IRC. The response-evaluable population will be used for the analyses of time to response, and duration of response (defined in patients with confirmed response and will be summarized descriptively). Patients have measurable disease defined by at least 1 of the following 3 measurements:

- Serum M-protein ≥ 1 g/dL (≥ 10 g/L).
- Urine M-protein ≥ 200 mg/24 hours.
- Serum free light chain assay: involved free light chain level ≥ 10 mg/dL (≥ 100 mg/L) provided the serum free light chain ratio is abnormal.

2.4 Per-Protocol (PP) population

The PP population is a subset of the ITT population. The PP population consists of all patients who do not have major protocol violations, as determined by the study clinician, who is blinded to study drug assignment. All decisions to exclude patients from the PP population will be made before the unblinding of the study.

The PP population will be used as a sensitivity analysis of the ITT population for the primary efficacy endpoint PFS if there are more than 5% patients are excluded from the ITT population.

3. HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

There is one primary endpoint in this study. (See section 5.7.2 for study treatment arms)

The null and alternative hypothesis for PFS is:

H_0: PFS in Arm MLN9708+LenDex= PFS in Arm LenDex

H_a: PFS in Arm MLN9708+LenDex > PFS in Arm LenDex

There are three key secondary efficacy endpoints in this study.

The null and alternative hypothesis for OS is:

H_0: OS in Arm MLN9708+LenDex = OS in Arm LenDex

H_a: OS in Arm MLN9708+LenDex > OS in Arm LenDex

The null and alternative hypothesis for CR rate during the treatment period is:

H_0: CR rate in Arm MLN9708+LenDex = CR rate in Arm LenDex

H_a: CR rate in Arm MLN9708+LenDex > CR rate in Arm LenDex

The null and alternative hypothesis for pain response rate (analyzed in patients with baseline worst pain score ≥ 4) is:

H_0: Pain response rate in Arm MLN9708+LenDex = Pain response rate in Arm LenDex

H_a: Pain response rate in Arm MLN9708+LenDex > Pain response rate in Arm LenDex

3.2 Statistical Decision Rules

A closed sequential testing procedure will be used to test the primary endpoints and all 3 key secondary endpoints with the following testing order:

1. PFS (primary endpoint) in the ITT population at the first or both IAs and PFS at IA2 in 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring expanded high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21);
2. OS (first key secondary endpoint) at the IAs or FA;
3. CR rate (second key secondary endpoint) at the IAs or FA; and
4. Pain response rate (third key secondary endpoint) at the IAs or FA.

OS will be tested at the IAs or FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). The proof of strong control of the Type I error rate for testing PFS and OS in the ITT population and PFS in the subgroup populations is shown in the appendix in the SAP. CR rate will be tested at the same alpha level as that for OS whenever OS reaches statistical significance. Pain response rate will be

tested at the same alpha level as that for CR rate whenever CR rate reaches statistical significance. Due to the closed sequential testing property, the family-wise type I error is strongly controlled for both the primary endpoint and key secondary endpoints.

All other efficacy endpoints will be tested at a 2-sided alpha level of 0.05.

4. INTERIM ANALYSIS

4.1 Interim Analysis

There are 2 planned IAs. The first IA will be performed when approximately 326 disease progression/death events have occurred. This IA is expected to occur approximately 45 months after the first patient is enrolled. If the test for PFS in the ITT population is statistically significant at the first IA, this will be the FA for PFS for statistical testing purposes, central efficacy and investigator assessments of disease response for protocol purposes will be discontinued (except for investigator assessment of PFS2) given that the primary endpoint has been met, and the second IA will be conducted for OS when approximately 250 death events have occurred. If the test for PFS does not reach statistical significance at IA1 in the ITT population, then at IA2 PFS will be tested in both the ITT population and in 3 prespecified subgroups, as described below.

The subgroup testing strategy approach includes 2 major components: a) preservation of the ability to detect the overall treatment effect using a reduced overall significance level of $\alpha_1 = 0.04$, which will be used for the ITT population, and b) test of treatment effect for the 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring expanded high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21). Subgroup testing will be conducted using the remaining $\alpha_2 = 0.01$ and the Hochberg procedure for multiplicity correction among the 3 prespecified subgroups (refer to the appendix in the SAP for proof of strong control of the Type I error rate). Because the size of the treatment effect may be substantially greater in a prespecified subgroup than in the overall study population, analysis of patients in each subgroup at a stringent significance level may still provide a statistically significant outcome. The detailed statistical design schema is presented in Figure 4-1.

CCI

[redacted]

For the testing of PFS in the ITT population, the Gamma(-1) alpha spending function will be used to calculate the significance boundary based on the observed number of PFS events with total alpha=0.04. The first IA will be performed when approximately 326 PFS events have occurred. This will be the first analysis for PFS for statistical testing purposes. If the test is statistically significant, then this analysis will be the FA of PFS for statistical testing purposes. No subsequent PFS testing will be conducted, and central efficacy and investigator assessments of disease response for protocol purposes will be discontinued except for the investigator assessment of PFS2 (see the Schedule of Events of protocol). In this scenario, the second IA will be for OS testing when approximately 250 death events have occurred and will determine whether the final number of OS events might be increased.

If the test for ITT PFS is not statistically significant at the first IA, response assessments will continue until IA2, and PFS testing in the ITT and subgroup populations will be conducted in parallel at the second IA, when approximately 370 PFS events have occurred (rather than the previous study design of 435 PFS events); this will be the FA of PFS for statistical testing purposes. If the test for PFS is significant at the second IA, OS will be tested, and determination of whether the final number of OS events will be increased from 320 to up to

400 will occur. If the test for PFS in the second IA is not statistically significant in any population (the ITT or any of the 3 subgroups), the study may be stopped.

Because at the time of this amendment, the boundary for ITT PFS at IA1 has already been calculated based on 328 PFS events observed at IA1, 435 PFS events targeted at PFS final analysis, and the Gamma(-1) alpha-spending function, this boundary will not be changed. However, the boundary for ITT PFS at IA2 (final analysis of ITT PFS) will be calculated based on the observed number of PFS events at IA2 in order to spend what is left of the overall alpha-level 0.04 for ITT. The final boundaries at IA1 and IA2 will not approximate a Gamma(-1) function, but type I error will remain protected under the flexible alpha-spending approach (see appendix in the SAP for more details).

For the testing of OS, alpha spending for IA1 and IA2 will always be based on the observed events (information fraction) using alpha=0.04 with a different adjustment of critical value at OS FA testing (CHW test statistics [3] will be used for the primary analysis of OS at FA) based on the following scenarios:

1. If ITT PFS is significant in IA1, then ITT OS will be tested in the FA with a total alpha of 0.04; there is no test on subgroup PFS.
2. If ITT PFS is not significant in IA1, then parallel testing of the ITT population PFS and the subgroup populations PFS will occur in IA2:
    a. If the ITT population's PFS is significant and at least 1 subgroup is not significant, then the ITT population's OS will be tested at IA2 and FA with potential sample size re-estimation using a total alpha of 0.04.
    b. If the ITT population's PFS is significant and all 3 subgroup populations' PFS are significant, then the ITT population's OS will be tested at IA2 and FA where the critical value at FA can be updated based on a total alpha of 0.05.
    c. If the ITT population's PFS is not significant and at least 1 subgroup population's PFS is significant, then no formal ITT OS testing will be conducted.

The family-wise error rate for the 4 null hypotheses for PFS and the 1 hypothesis for OS for the overall study population is controlled using a prespecified, 2-sided 0.05 level of significance. The proof of strong control of the Type I error rate for testing PFS and OS in the ITT population and PFS in the subgroup populations is shown in the appendix in the SAP. For the other 2 key secondary endpoints, the CR rate will be tested at the same alpha

level, instead of the same critical value, as that of the OS analysis when OS reaches statistical significance. The pain response rate will be tested at the same alpha level as that of the CR rate analysis when the CR rate reaches statistical significance. Because of the closed sequential testing property, the family-wise error rate is strongly controlled for both the primary endpoint and the 3 key secondary endpoints [4].

The IAs will be conducted by the independent statistical center (ISC) and presented for review to the IDMC. During the closed session of the IDMC meeting at IA2, the IDMC will compare the conditional power for OS based on the interim result with the prespecified adaptation rules and recommend to the sponsor executive committee the final adaptation decision on OS. The adaptation rule will be included in the appendix of IDMC charter and can only be accessed by ISC, IDMC, Head of Biostatistics and the sponsor design statistician who are not involved in the study conduct. This recommendation will be documented in the IDMC closed meeting minutes.

4.2 Independent Data Monitoring Committee (IDMC)

An IDMC supported by an independent statistician will review safety at regular intervals additionally safety and efficacy data at 2 planned interim analyses. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on the IDMC recommendation, Millennium will notify the appropriate regulatory authorities. In addition, the IDMC will periodically review safety data at regularly scheduled meetings prespecified in the IDMC charter.

The first formal safety review will occur after approximately 60 subjects have been randomized and receive at least 1 cycle of study treatment. Subsequently, periodic safety reviews will also occur as prespecified in the IDMC charter.

Study accrual will not be interrupted due to the scheduled safety reviews. The IDMC or MLN9708 study team may request an ad hoc meeting for any reason, including a significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, subject incidence rates of AEs (including all serious AEs, treatment-related AEs, serious treatment-related events, and events requiring the discontinuation of study drug) will be tabulated by System Organ Class, preferred term, and severity grade. Listings and/or narratives of "on-study" deaths and other serious and significant AEs, including any early withdrawals due to AEs, will be provided.

Records of all meetings will be archived. The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Millennium. Further details will be provided in the IDMC charter.

4.3 Independent Review Committee (IRC)

An independent review committee (IRC) will review all blinded disease evaluation data from the study and determine disease status (response and progression). Data from the IRC will not be provided back to the investigator during the conduct of the study. Likewise, investigator response assessments will not be provided to the IRC.

5. STATISTICAL METHODOLOGY

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

5.1 Sample Size Justification

The primary objective of this study is to determine if MLN9708 plus lenalidomide and dexamethasone improves PFS compared with placebo plus lenalidomide and dexamethasone in patients with newly diagnosed MM. The study will not be stopped after the PFS analysis, however, even if a significant PFS is observed, in order to obtain an adequate statistical power for OS.

The total sample size was calculated based on maintaining 80% power to test the OS. The study is also adequately powered to test PFS. There is 2 planned IA and 1 FA.

Assuming a hazard ratio of 0.70 (median PFS of 25 months in control arm versus 35.8 months in treatment arm), 370 PFS events will be needed (92% power and 2-sided alpha of 0.04) with up to 2 planned PFS analyses conducted as described in the section 4.1.

The first IA will be performed when approximately 326 PFS events have occurred. This is expected to occur approximately 45 months after the first patient is enrolled, including a 27-month enrollment period and additional 18-month follow-up from the last patient.

If the test for PFS in the ITT population is statistically significant at the first IA, this will be the FA for PFS for statistical testing purposes, and the second IA will assess OS when approximately 250 death events have occurred.

If the test for PFS in the ITT is not statistically significant at the first IA, then the second IA will assess PFS and OS when approximately 370 PFS events have occurred. In addition, in such a case, PFS will be tested at IA2 in 3 prespecified subgroups: 1) patients with baseline CrCl > 60 mL/min; 2) patients aged < 75 years; and 3) patients harboring expanded high-risk cytogenetic abnormalities defined as del(17p), t(4;14), t(14;16), and amp(1q21).

For the final OS analysis, the total event size calculation will be based on the adaptive sample size re-assessment approach.[3, 5] The minimum event size of 320 death events is based on an optimistic assumption of a hazard ratio of 0.72 (median survival of 50 months in the control arm vs 69.4 months in the treatment arm) with 80% power at a 2-sided 0.05 level of significance. The O'Brien-Fleming alpha spending function (the Lan-DeMets method) will be used to calculate the significance boundary based on observed number of death events in each IA with a total of 320 OS events for the FA. In the second IA, if OS significance is not claimed, the conditional power based on OS will be calculated. If the conditional power falls in the favorable zone or unfavorable zone, the FA of OS with approximately 320 events will remain unchanged. If the conditional power falls in the promising zone, the event size will be determined according to a prespecified sample size adaptation rule, with an event cap of 400 OS events. No futility analysis will be performed in the study.

5.2 Randomization and Stratification

Randomization scheme will be generated by an independent statistician at Millennium who is not on the study team. Prior to dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an interactive voice/ web response system (IXRS).

Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms, stratified by: age (<75 years vs ≥ 75), ISS (stage 1 or 2 vs stage 3), and BPI-SF worst pain score (< 4 vs ≥ 4) at screening.

5.3 Blinding and Unblinding

This is a double-blind study: all study personnel including the investigators, site personnel, study clinicians, and the sponsor will be blinded to the treatment assignments for the duration of the study. Only the independent statistical center (ISC) and IDMC will have access to un-blinded individual patient level data. The periodic safety analyses will be generated for the IDMC by an ISC. The formal interim efficacy analyses will also be conducted by ISC for the IDMC.

Refer to section 4.2 for the roles and responsibilities of IDMC.

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. For patient reported outcomes data, primarily missing data imputation will be based on published instrument specific methods. Other missing data imputation method such as Last Observation Carry Forward (LOCF) and multiple imputation method may be explored as sensitivity analyses for patient reported outcomes data.

For the key secondary endpoints CR rate, missing value is defined as no post-baseline response assessment either due to lost to follow-up or withdrawal by patient. In the primary analysis, if the response assessment in either arm is missing on comparing response rates, it will be counted as a failure (non-responder) instead of a missing value. The procedure to deal with missing data in the primary analysis for the pain response rate will be using the same method as CR rate.

5.4.1.1 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded in the screening visits.

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the 15th will be used.

- If only a year is present, and it is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicates that the date is earlier.

- If only a year is present, and it is not the same as the year of the first dose of study drug, the 15th of June will be used, unless other data indicates that the date is earlier.

5.4.1.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies

Every effort will be made to avoid missing/partial dates in on-study data.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If the stop date has month and year but day is missing, the last day of the month will be imputed
- If the stop date has year, but day and month are missing, the 31th of December will be imputed

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

Adverse events with start dates that are completely or partially missing will be imputed as follows:

- If the start date has month and year but day is missing, the first day of the month will be imputed
    - If this date is earlier than the first dose date, then the first dose date will be used instead

  - If this date is later than the stop date (possibly imputed), then the stop date will be used instead

- If the start date has year, but day and month are missing, the 15th of June will be imputed
  - If this date is earlier than the first dose date, then the first dose date will be used instead
  - If this date is later than the stop date (possibly imputed), then the stop date will be used instead

If the start date of an event is completely missing, then it is imputed with the first dose date.

Concomitant therapies with start dates that are completely or partially missing will be analyzed as follows:

- If the start date has month and year but day is missing, the therapy will be included in the summary table if the month and year of the start date of the event are:
  - On or after the month and year of the date of the first dose of study drug

  and

  - On or before the month and year of the date of the last dose of study drug plus 30 days.
- If the start date has year, but day and month are missing, the therapy will be included in the summary table if the year of the start date of the event is:
  - On or after the year of the date of the first dose of study drug

  and

  - On or before the year of the date of the last dose of study drug plus 30 days.

If the start date of an event is completely missing, then the therapy will be included in the summary table.

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing,
  - If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.

- If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month is imputed.

- When only a year is present,
  - If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.
  - If the onset year is not the same as the year of last dose with study drug, the first day of the year is imputed.

- If no components of the onset date are present the date of last dose + 1 will be imputed.

5.4.2 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration.

5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

5.4.4 Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

5.4.5 Withdrawals, Dropouts, Loss to Follow-up

Time to event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events (progressive disease / death). Rules for censoring are detailed in section 5.8.

5.5 Patient Disposition

Patient disposition includes the number and percentage of patients for the following categories: patients in each of the study populations, patients discontinued from the treatment, primary reason to discontinue from the treatment, patients discontinued from the study, and primary reason to discontinue from the study. All percentages will be based on the number of patients in the ITT population.

A listing will present data concerning patient disposition.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Demographics will be summarized by treatment groups in a descriptive fashion in the ITT population. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and other parameters as appropriate. Patient enrollment by region and country will also be summarized by treatment groups.

5.6.2 Medical History

General medical history and prior medications will be listed for all patients.

Medical history will be summarized (frequency and percentage) for both treatment groups by the disease categories recorded in the database. A patient is counted only once within a category. Percentages are based on the number of patients in the safety population within each treatment group.

5.6.3 Baseline Disease Status

Baseline disease characteristics (Eastern Cooperative Oncology Group [ECOG]) performance status, co-morbidity status by age (<65, 65≤ age <75, ≥75), type of myeloma, ISS stage, serum M-protein, urine M-protein, β_2-microglobin by category (ie, < 2.5, 2.5-5.5, > 5.5 mg/L), serum creatinine and its category (≤ 2, >2 mg/dL), creatinine clearance by category (ie, >30-60, >60 mL/min), serum albumin by category (ie, < 3.5, ≥ 3.5 g/dL), corrected calcium, Durie-Salmon stage, Lytic bone lesions, extramedullary disease will be summarized for all patients. Months from initial diagnosis to first dose of MLN9708 will be summarized for all patients if there is sufficient data for analysis.

A patient's type of myeloma is determined by the combination of heavy chain type (IgG, IgA, IgM, IgD, IgE, and other) and light chain type (Kappa, Lambda, and biclonal). In descriptive summaries, Myeloma type will be summarized separately for the heavy chain patients (according to IgG, IgA, IgM, IgD, IgE, biclonal, other) and for the light chain patients (according to kappa or lambda or biclonal).

Creatinine clearance is to be calculated using the Cockcroft-Gault formulas as follows:

For male patients:

$$\text{creatinine clearance} = \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

For female patients:

$$\text{creatinine clearance} = 0.85 \times \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

Integer values will be used.

Months from diagnosis to the randomization date for each treatment is calculated by

$$\frac{\text{randomization date - date of diagnosis}}{365.25/12}$$

Distribution of stratification factors will also be summarized.

5.6.3.1 Extent of disease at baseline

The following categories of extent of disease at baseline will be summarized: number of patients with bone marrow aspirate, bone marrow aspirate results (% plasma cells, % megakaryocytes present), number of patients with bone marrow biopsy, bone marrow biopsy results (% plasma cells, % cellularity, type of cellularity, % Kappa/Lambda ratio performed), skeletal survey results and imaging including Magnetic Resonance Imaging/ Computed Tomography/PET-CT results (normal, abnormal not clinically significant, abnormal clinically significant, and not done), number and percentage of present lytic bone lesions, number of extramedullary plasmacytoma, type of extramedullary plasmacytoma.

Percentage for all categorical summarizations for bone marrow biopsy/aspirate and aspirate is based on patients with an adequate sample for the specified test.

5.6.4 Bone Marrow Cytogenetic Results at Baseline

Bone marrow cytogenetic results at baseline from the conventional/karyotype and molecular/FISH cytogenetic analyses methods will be displayed. The results will be categorized as "Normal", "Abnormal" and "Indeterminate". The percentage of each category will be summarized.

The following are the categories of interest:

1. Del 17 positive group (made up of del 17 alone or in combination with t(4;14) or t(14;16) or amp(1q21))

2. t(4;14) alone [no del 17, t(4;14), t(14;16) or amp(1q21)]

3. t(14;16) alone [no del17, t(4;14), t(14;16) or amp(1q21)]

4. amp(1q21) alone [no del17, t(4;14) or t(14;16)]

5. High risk group: made up of del17, t(4;14) or t(14;16)

6. Expanded High risk group: made up of del17, t(4:14), t(14;16) or amp(1q21)

Standard risk group definition will differ for the high risk and the expanded high risk group and will be defined as patients for whom the tests for del17, t(4;14), t(14;16) and amp(1q21) are normal. Detailed definitions are listed in the section 5.8.1.1 on definition of subgroup.

Abnormal types of interest, including but not limited to del 13, del 17, t(4;14), t(14;16), will also be tabulated.

5.7 Treatments and Medications

5.7.1 Concomitant Medications

Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from the first dose through the end of the on-treatment period will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug preferred term for each treatment group in the safety population. By-patient listing will also be presented for concomitant medications.

Concomitant procedures will not be coded, but will be presented in a data listing in the safety population.

Types of subsequent therapy will also be summarized accordingly in the table and listing.

5.7.2 Study Treatments

Following the Screening period, patients who will be enrolled and treated with lenalidomide plus dexamethasone will be randomized to receive a study drug in a double-blind fashion, either MLN9708 or placebo. Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms.

Arm MLN9708+LenDex: Patients will receive MLN9708 4.0 mg capsule on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle.

Arm LenDex: Patients will receive placebo capsule on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle.

In both arms, patients over 75 years of age will receive reduced dexamethasone dose (20mg). Dose modifications may be made throughout the study based on toxicities. Patients with a low creatinine clearance ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) will receive a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

Patients may continue to receive treatment as outlined previously for 18 cycles (approximately 18 months), or until progressive disease (PD) or unacceptable toxicity, whichever comes first. After 18 cycles, patients will continue treatment in the same randomization arm on the same schedule with modified dose levels of the study drug and LenDex: reduce MLN9708 (or placebo) dose to 3.0 mg, reduce lenalidomide dose to 10 mg, and no dexamethasone.

5.7.2.1 Duration of Follow-up

The duration of follow-up is defined as time from randomization to the death or last known visit. If a subject dies, the duration equal to date of death minus study start + 1 with censor variable =1 (censored for follow up). If a subject is alive, the duration equal to the date subject last known to be alive minus study start + 1 with censor variable=0 (event for follow up).

Duration of follow-up for maintenance portion is defined as time from the date of first dose of maintenance to the death or last known visit.

5.7.2.2 Extent of Exposure

An overall summary of drug exposure will be presented including number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, …, and ≥36 treated cycles, for each treatment group in the safety population. Aggregate summary of numbers and percentages of patients who had 1-6, 7-12, 13-18, 19-24, 25-30, 31-36, ≥37 treated cycles will also be

presented in the same table. Extent of Exposure (days), which is calculated as (Last Dose Date of study drug – First Dose Date of study drug + 1), will also be presented.

Additionally exposure to dexamethasone will be characterized by total amount of dose taken in mg, total number of dose taken, number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, …, and ≥36 treated cycles, and relative dose intensity (%) for each treatment group in the safety population. Aggregate summary of numbers and percentages of patients who had 1-6, 7-12, 13-18, 19-24, 25-30, 31-36, ≥37 treated cycles will also be presented in the same table.

MLN9708 and lenalidomide exposure will be summarized similarly as dexamethasone for the applicable treatment group/option.

A treated cycle is defined as a cycle in which the patient received any amount of any study drug.

A treated cycle for a specific drug is defined as a cycle in which the patient received any amount of the specific drug.

Relative dose intensity (RDI) (%) is defined as 100 x (total dose received in mg) / (sum of prescribed dose over all treated cycles). For prescribed dose, if patients with a low creatinine clearance ≤ 60 mL/min received reduced lenalidomide dose of 10 mg at C1D1, then 10 mg will be used in the denominator per protocol dosing administration. Similarly, 20 mg will be used for Dexamethasone RDI calculation for patients over 75 years old. After 18 cycles, MLN9708 will be reduced to3 mg, Len will be reduced to 10 mg daily and Dex will be discontinued, so prescribed dose per protocol will be updated and reflected in the calculation accordingly.

Dosing data will also be presented in a by-patient listing.

5.7.2.3 Treatment Modifications

Action on each study drug will be summarized by each of the Cycle 1 through 36, sum of the remainder Cycles, Cycles 1-6, Cycles 7-12, Cycle 13-18, Cycles 19-24, Cycle 25-30, Cycle 31-36, >=37 and total for each treatment group in the safety population.

5.8 Efficacy Analyses

All efficacy evaluations will be conducted using the ITT population unless otherwise specified.

5.8.1 Primary Efficacy Endpoint

There is 1 primary endpoint: PFS, which is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first. Patients without documentation of PD will be censored at the date of last response assessment. The details regarding the handling of missing assessment and censoring for PFS analysis are presented in Table 5-1.

Table 5-1 Handling of Missing Assessment and Censoring for PFS Primary Analysis based on FDA guidance

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no post baseline assessment, no subsequent anticancer therapy after study treatment, no death	Date of Randomization	Censored
Disease progression documented between scheduled visits	Date of documented disease progression	Event
No documented death or disease progression	Date of last adequate assessment*	Censored
Lost to follow-up, withdraw consent before any documented death or disease progression	Date of last adequate assessment*	Censored
Death or progression after more than one missed visit	Date of last adequate assessment*	Censored
Alternate antineoplastic therapy started prior to disease progression	Date of last adequate assessment prior to starting alternate antineoplastic therapy	Censored
Death before first assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event

* Adequate disease assessment is defined as there is sufficient data to evaluate a patient's disease status.

5.8.1.1 Primary Efficacy Analysis

PFS will be analyzed when approximately 326 PFS events have occurred. A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.05. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The Kaplan Meier (K-M) survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Sensitivity analyses for PFS include:

1. PFS assessed by investigator will be analyzed in the ITT population.

2. PFS assessed by IRC will be analyzed in the per protocol population.

PFS assessed by IRC using different censoring mechanisms will be analyzed in the ITT population, for example, not censoring for patients who discontinue treatment and go on transplant or alternative antineoplastic therapy. The other details of the handling of missing assessment and censoring for additional sensitivity analyses are presented in Table 5-2. Sensitivity analyses will be performed on the basis of one alteration at a time, not on combined alterations unless specified otherwise. Additional sensitivity analysis for PFS might be conducted on treating start date of alternate antineoplastic therapy as events.

Table 5-2 Handling of missing assessment and censoring for PFS Sensitivity Analysis based on EMA guidance

Situation	Date of Progression or Censoring	Outcome
Alternate antineoplastic therapy started prior to disease progression	Date of documented disease progression	Event
Death or disease progression after more than one missed visit	Date of death or disease progression	Event

Subgroup analyses will be performed for PFS relative to baseline stratification factors, demographic data such as sex, race, region (e.g. North America, Europe and Other), and disease characteristics, and CCI [redacted] The details on subgroups are presented in the following:

Subgroup	Definition of Group
Age	< 75 years, ≥ 75 years
Sex	male vs female
Race	white, black-African American, Asian, other
Region	North America, Europe, APAC, other
Cytogenetic risk	Standard-risk[1], high-risk [(del17); t(4;14); t(14;16)], not available Standard-risk[2], expanded high-risk [(del17); t(4;14); t(14;16); amp(1q21)], not available
ISS stage	In additional to stratification factors , also define as I or II or III
Renal function based on baseline creatinine clearance	< 60 mL/min, and ≥60 mL/min
ECOG performance status	0 or 1 vs 2
CCI [redacted]	[redacted]

1. Standard Risk in this analysis is defined as del (17), t(4:14) and t(14:16) normal
2. Standard Risk in this analysis is defined as del (17), t(4:14) , t(14:16) and 1q 21 normal

5.8.2 Key Secondary Efficacy Endpoints

There are 3 key secondary endpoints: CR rate, OS and Pain response rate.

Overall Survival

OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed based on the ITT population.

CR Rate

The CR rate is defined as the proportion of patients who achieve CR assessed by an IRC relative to the ITT population during the treatment period. If the response assessment in either arm is missing on comparing CR rates, it will be counted as a failure (non-responder) instead of a missing value.

Pain Response Rate

Pain response is defined, among patients whose baseline pain score are >=4, as the occurrence of at least a 30% reduction from baseline in BPI-SF worst pain score over the last 24 hours without an increase in analgesic use for 2 consecutive measurements >=28 days apart.

5.8.2.1 Key Secondary Efficacy Analysis

Three key secondary efficacy endpoints will be tested sequentially in the order of 1) OS; 2) CR rate; 3) Pain response rate. OS will be tested at the IAs or FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). CR rate will be tested at the same alpha level as that for OS whenever OS reaches statistical significance. Pain response rate will be tested at the same alpha level as that for CR rate whenever CR rate reaches statistical significance. Due to the closed sequential testing property, the family-wise type I error is strongly controlled for both the primary endpoint and key secondary endpoints.

Overall Survival

A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to OS. The test significance level at the IA and FA is decided by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). In addition, an unadjusted stratified Cox

model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

To adjust for the potential confounding effects of subsequent therapies after patients discontinue study treatment, the following 2 methods will be used:

- Marginal Structural Models (MSMs) by Robins and Finkelstein [2000]
- Inverse Probability of Censoring Weighted (IPCW) method by Robins and Finkelstein [2000]

In the MSM and IPCW analyses, in order to derive weights adjusting for the time-fixed and time-varying confounding effects due to taking alternative therapies, the covariates that affect disease progression and post-progression treatment, and the OS endpoint will be used. Baseline covariates include region (North America, others), age (< 75, ≥ 75), race (white, non-white), ECOG score (0 or 1, 2), type of myeloma (IgA, other), presence of extramedullary plasmacytomas (yes, no), presence of lytic bone lesions (yes, no), cytogenetic abnormalities (high risk, others), baseline hemoglobin, baseline platelets, baseline creatinine clearance, baseline albumin, baseline LDH, baseline β_2 microglobulin, and baseline corrected calcium. Time-varying covariates include duration of exposure, disease progression status at each study visit, hemoglobin value at each study visit and progression/relapse, platelets value at each study visit and progression/relapse, M-protein value at each study visit and progression/relapse, and MRD status over time. The final criteria for selected covariates would need to be statistically have a p-value of less than or equal to 0.1 in the multivariate logistic regression models for weight calculations. If there are more than 5% missing in the baseline covariate, then this covariate will be dropped from the weighting calculation and final OS model. For both MSM and IPCW analyses, logistic regression models on repeated measurements will be used to approximate the Cox models in the weight derivations from which stabilized weights will be derived per subject per observation. SAS proc PHREG procedure with counting process type of data input, which takes multiple observations per subject, will be used as the final Cox model for OS for both MSM and IPCW approaches, where robust variance will be used to accommodate covariance introduced by correlated longitudinal observations within each subjects and other extra variabilities due to departure from model assumptions. Adjusted HRs, their

corresponding 95% confidence intervals, and adjusted p-values will be presented. Specific to MSM, interaction between active treatment and alternative therapy will be included in the final model if the p-value for this term is <0.1. For IPCW, adjusted K-M curves will be presented.

Subgroup analyses will be performed for OS, similarly as detailed in section 5.8.1.1 of PFS analysis.

CR Rate

CR rate will only be tested after statistical significance is achieved for PFS and OS. Stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare CR rates between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of odds ratio. The odds ratio and its associated 95% CIs will be presented.

Sensitivity analyses for CR rate include but are not limited to:

1. Response assessed by investigator in the ITT population

2. Response assessed by IRC in the per protocol population

3. Response assessed by IRC in the response evaluable population

Pain Response Rate

If CR is significant, then Pain response rate will be analyzed in patients with baseline worst pain score ≥ 4 in the ITT population. Pain response rate is the proportion of patients who have a pain response and will be summarized by treatment groups. If the pain assessment in either arm is missing on comparing pain response rates, it will be counted as a failure (non-responder) instead of a missing value. The stratified CMH test will be used to compare the 2 treatment arms. In addition, the absolute treatment difference in pain response rate will be provided, along with 95% CI.

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5.8.3 Other Secondary Efficacy Endpoints and Analyses

Other secondary efficacy parameters include overall response rate (ORR) , time to response (TTR), time to progression, duration of response, OS and PFS in high-risk population defined by del(17), and translocation t(4;14) and t(14;16) (at least one of these abnormalities), and expanded high-risk population defined as del(17), amp(1q21), and translocation t(4;14) and t(14;16) (at least one of these abnormalities)

Disease response-related endpoints will be analyzed using IRC-assessed response rate.

ORR

ORR is defined as the proportion of patients who achieved PR or better relative to the ITT population. ORR will be analyzed based on the ITT population using the method similar to that used in the CR rate analysis. Additional analysis will also be presented for CR+VGPR.

Time to Response

Time to response is defined as the time from randomization to the first documentation of PR or better. Time to response will be compared in the ITT population and summarized descriptively for the responders.

Time to Progression

TTP is defined as the time from the date of randomization to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of last response assessment that is SD or better. TTP will be analyzed based on the ITT population using the similar method as PFS.

Duration of Response

DOR is defined as the time from the date of first documentation of a PR or better to the date of first documentation of PD for responders. Responders without documentation of PD will be censored at the date of last response assessment that is SD or better. DOR will be summarized descriptively using the Kaplan-Meier method.

Progression-free survival 2

Progression-free survival 2 (PFS2) is defined as the time from the date of randomization to the date of first documentation of PD on the next antineoplastic therapy following study treatment or death due to any cause, whichever occurs first.

PFS2 will be analyzed based on the ITT population. A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS2 at a 2-sided alpha level of 0.05. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The Kaplan Meier (K-M) survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

The details of the handling of missing assessment and censoring are presented in Table 5-3 and Table 5-4.

Table 5-3 Censoring for PFS2 For Those Who have Received Second line Therapy following Study Treatment

Situation	Date of Progression or Censoring	Outcome
Documented death or disease progression during second line therapy	Date of death/disease progression	Event
No documented death or disease progression during second line therapy	Date of last disease assessment	Censored
Lost to follow-up, withdraw consent before any documented death or disease progression during second line therapy	Date of last disease assessment	Censored
Start of third line therapy prior to the disease progression during second line therapy	Date of last disease assessment prior to starting the third line therapy	Censored

Table 5-4 Censoring for PFS2 for Those Who have not received Second Line of Therapy

Situation	Date of Progression or Censoring	Outcome
No documented death	Date of last visit	Censored
Death	Date of death	Event

Clinical Outcomes in High-Risk Population

Overall survival, PFS, ORR and DOR in the high-risk subgroups will be analyzed using a similar method as those in the ITT population. The following high-risk populations will be analyzed:

- By individual abnormality group within high risk: patients carrying 1 of the following cytogenetic abnormalities: del(17), translocation t(4;14), t(14;16)

- the del17 will include pts with del17 alone along with pts where the del17 is associated to t(4;14),or t(14;16)
- the t(4;14) group will include ONLY pts with t(4;14) ALONE (no del17, t(14;16))
- the t(14;16) group will include ONLY pts with t(14;16) ALONE (no del17, t(4;14))

- By individual abnormality group within expanded high risk: patients carrying 1 of the following cytogenetic abnormalities: del(17), translocation t(4;14), t(14;16) or amp(1q21)
  - the del17 will include pts with del17 alone along with pts where the del17 is associated to t(4;14),or t(14;16) or amp(1q21)
  - the t(4;14) group will include ONLY pts with t(4;14) ALONE (no del17, t(14;16) or amp(1q21))
  - the t(14;16) group will include ONLY pts with t(14;16) ALONE (no del17, t(4;14); or amp(1q21)))
  - the amp(1q21) group will include ONLY patients with amp(1q21) ALONE (no del17, t(4;14) or t(14;16))
- Cytogenetic high-risk group defined as patients carrying any of the following cytogenetic abnormalities: del(17), translocation t(4;14), or t(14;16)
- Cytogenetic expanded high-risk group defined as: patients carrying any of the following cytogenetic abnormalities: del17, t(4;14), t(14; 16) or amp(1q21)

5.9 Pharmacokinetic and Biomarker Analysis

5.9.1 Pharmacokinetic Analyses

Plasma concentration-time data will be presented in listings. PK data will be used to perform population PK analysis using a nonlinear mixed effects modeling approach and to assess the effect of various covariates on PK after including data from other studies, if

possible. The analysis plan for the population PK analysis will be separately defined and the results of these analyses will be reported separately.

5.9.2 Biomarker Analysis

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[redacted]

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5.9.3 Minimal Residual Disease Analysis

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[redacted]

5.10 Analyses of Patient-Reported Outcomes and Health Economics

5.10.1 Patient Reported Outcomes (PROs)

Patient-reported outcome (PRO) assessments using the EORTC QLQ-C30 and the MY20 will be analyzed using ITT population. The descriptive statistics of actual value and change from baseline of the subscale scores for EORTC QLQ-C30 and MY20 will be summarized by treatment group over time. Additionally, the descriptive statistics of actual values and changes from baseline of global health status/quality of life (QOL) will be summarized by treatment group over time for responders and then nonresponders. The subscales of EORTC QLQ-C30 and MY20 are defined as shown in Table 5-5 and Table 5-6.

Table 5-5 Definition of Subscale Scores of EORTC QLQ-C30

Subscale	Individual Items
Physical functioning	1-5
Role functioning	6-7
Emotional functioning	21-24
Cognitive functioning	20, 25
Social functioning	26-27
Quality of life	29-30
Fatigue	10, 12, 18
Nausea and vomiting	14-15
Pain	9, 19
Dyspnea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial difficulties	28

Table 5-6 Definition of Subscale Scores of EORTC QLQ-MY20

Subscale	Individual Items
Future perspective	18-20
Body image	17
Disease symptoms	1-6
Side effects of treatment	7-16

Differences between treatment groups in the EORTC QLQ-C30 and MY20 subscale scores will be evaluated using published minimally important difference (MID) values. Patients with a change from baseline score ≥MID in a direction reflecting deteriorating functioning or increased symptoms at a given time point will be classified as "worsened", whereas those with a change for better of ≥MID will be classified as "improved". Those with a change from baseline score within MID will be classified as "stable". The number and percentage of patients with a change from baseline in subscale scores >=MID and <= -MID will be summarized by treatment group over time. Specific interest centers on physical functioning, global quality of life, fatigue, nausea/vomiting, pain, dyspnea, appetite loss, and constipation/diarrhea. The main endpoint for the PRO analysis will be the global health status/quality of life subscale of the EORTC QLQ-C30 and functional scales and symptom

scales of MY20. The other PRO endpoints include the remaining EORTC QLQ-C30 and MY20 subscale scores. The change from baseline in subscale scores at Cycle 18 will be presented using cumulative distribution function (CDF) figures. Additionally, CDF curves will be generated for global health status/quality of life score change from baseline at Cycle 18 by treatment group among responders and non-responders, respectively.

The change from baseline in subscale scores will be also analyzed using the repeated measures linear mixed effects models, including treatment group, baseline score, ISS stage at screening, age, sex and race as covariates. The repeated-measures analysis will use measurements collected from all available time points specified in the schedule of events in the protocol. Estimation of the variance- covariance matrix and statistics such as Akaike information criteria (AIC), Bayesian information criteria (BIC) will be included in evaluating the linear mixed-effects model. The 95% confidence intervals of the difference of the changes from baseline between the two treatments will also be provided.

Details of scoring and initial handling of missing data are included in the EORTC QLQ-C30 and MY20 scoring guidelines.

Missing data pattern will be examined. As sensitivity analyses, different imputation methods for missing data including Last Observation Carry Forward (LOCF), random slope model, and pattern mixture model may be performed if appropriate after examining missing data patterns.

5.10.2 Health Economics Analysis Using Medical Resource Utilization and Utility

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5.10.3 Pain

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Pain progression is defined as the occurrence of 1 of the following and confirmed by 2 consecutive evaluations (To qualify as progression, the patient must have a BPI-SF worst pain score ≥ 4 during pain progression):

- A ≥ 2 point and 30% increase from baseline in BPI-SF worst pain score without an decrease in analgesic use, or
- A 25% or more increase in analgesic use from baseline without a decrease in BPI-SF worst pain score from baseline

Analgesic use can be stable or increased according to the following definitions:

- Stable analgesic use is defined as less than a 25% change of the oral morphine equivalent (OME) dose from baseline
- Increased analgesic use is defined as an increase of 25% or more in OME from baseline

A sensitivity analysis will be conducted on pain progression without confirmation by 2 consecutive assessments.

In addition, the actual value and change from baseline of BPI-SF pain scores will be summarized by treatment group over time. The change from baseline in worst pain score

will be also analyzed using the repeated measures linear mixed effects models, including treatment group, baseline score, ISS stage at screening, sex, race, and age as covariates.

5.11 Safety Analyses

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to the study drug regimen and reasons for discontinuation will be tabulated.

5.11.1 Adverse Events

5.11.1.1 Adverse Events

Adverse events will be coded using MedDRA. All AEs will be presented in a by-patient listing. Treatment-emergent AEs are AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.

AEs will be tabulated according to the MedDRA by system organ class, high level terms and preferred terms and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs (also report Grade 3 and 4 separately)
- Grade 3 or higher drug-related treatment-emergent AEs (also report Grade 3 and 4 separately)
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of patients in either treatment group)
- SAEs

Patients with the same AE more than once will have that event counted only once within each body system, once within each high level term, and once within each preferred term.

Drug-related treatment-emergent AEs will also be summarized by the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 4.03. Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, once within each high level term, and once within each preferred term.

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of any treatment arm) will be tabulated by preferred term. Patients with the same AE more than once will have that event counted only once within each preferred term.

An overall summary AE table will include numbers and percentages of patients who had any AE, drug-related AE, grade 3 or higher AE, grade 3 or higher drug-related AE, serious AE (SAE), drug-related SAE, AE resulting in discontinuation, and on-study deaths. On-study death is defined as the death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug.

Development of new or worsening of existing SREs (eg, new fractures, irradiation of or surgery on bone, or spinal cord compression) from baseline through the development of PD will be summarized and presented.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Two types of incidence rates will be calculated for the safety population based on the new primary malignancy assessment:

- Incidence proportions, defined as the percentage of the subjects reporting any new primary malignancy in the safety population with available information
- Incidence rates, defined by the number of the subjects reporting any new primary malignancy divided by the total duration of follow-up (patient-years = pt-yrs) in the safety population with available information up to the onset of new primary malignancies

For incidence proportions, the relative risks, defined as the ratio of incidence proportions between the 2 randomized treatment groups, were provided along with their 95% CIs. For incidence rates, the relative risks, along with their 95% CIs, will be calculated using an exponential regression model for lifetime data (assuming constant hazards).

Due to the distinct nature of hematologic and nonhematologic neoplasms, as well as the emerging signals of new primary malignancies for immunomodulating agents, analyses of new primary malignancies may be performed separately for hematologic and nonhematologic malignancies.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN9708.

Time to Resolution and Improvement of Peripheral Neuropathy Events

Peripheral neuropathy is defined as the treatment emergent adverse event in the high-level term of peripheral neuropathies NEC according to MedDRA.

A PN event is considered as resolved if its final outcome is resolved with no subsequent PN event of the same preferred term occurring on the resolution date or the day before and after. A PN event is considered as improved if the event improves from the maximum grade. That is, all the grades recorded after the maximum grade is less than the maximum grade.

Time to resolution and time to improvement are to be defined for each PN event. Time to resolution is defined as the time from the initial onset date (inclusive) to the resolution date for resolved events. Time to improvement is defined as the time from the initial onset date (inclusive) of the maximum grade to the first onset date that the toxicity grade is below the maximum grade with no higher grade thereafter, or the resolution date, whichever occurs first.

Time to improvement and time to resolution of PN events will be summarized by outcome (improvement or resolution) using the Kaplan-Meier method. The K-M survival curve and K-M medians (if estimable), along with their 2-sided 95% CIs, will be presented. This analysis is event based, thus 1 subject could contribute multiple observations if the subject has more than 1 PN event.

The analysis may be conducted for patients with any PN events or those with grade ≥ 2 PN event or those with grade ≥ 3 PN event, respectively, if data permits.

5.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment-emergent SAE will be summarized by MedDRA primary system organ class, high level term, and preferred term. Drug-related SAE will be summarized similarly.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent AE status).

5.11.1.3 Deaths

A by-patient listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status).

5.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug regimen will be presented.

5.11.2 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. However, for the bone marrow plasma cell percentage, the convention as (x-1)% (mainly for < 5% for CR) will be used.

Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratory will only be used when no central laboratory test results exist at the same scheduled sample collection time point.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. Unscheduled laboratory test results will be listed and included in laboratory shift tables. The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, ANC, ALC, platelets, and white blood cell (WBC) count
- Serum chemistry: blood urea nitrogen, creatinine, total bilirubin, uric acid, LDH, albumin, alkaline phosphatase, AST, ALT, glucose, calcium, sodium, potassium, magnesium, phosphate, and PT.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity (version 4.03) from baseline to post baseline worst CTC grade. Parameters to be tabulated will include:

- Hematology: ALC, ANC, hemoglobin, platelets, WBC
- Serum chemistry: ALT, AST, alkaline phosphatase, creatinine, total bilirubin, calcium, magnesium, potassium, sodium, and phosphate.

Mean laboratory values over time through Cycle 36 for key lab parameters will be produced, including but not limited to ANC, platelets, and liver function tests (ALT/SGPT, AST/SGOT, alkaline phosphatase, and total bilirubin).

By-patient listings to be presented include hematology, serum chemistry, urinalysis, urine total protein, and urine creatinine.

5.11.3 **Electrocardiograms**

Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time point.

QTc interval will be calculated using Bazett's correction and Fridericia's correction, if necessary. The formulas are:

$$QTc\ (Bazett) = QT / (RR^{0.5})$$

$$QTc\ (Fridericia) = QT / (RR^{0.33})$$

where RR = 60 / heart rate (bpm)

In addition, a categorical analysis of QTc intervals will be performed for each time point. The number and percentage of patients in each QTc interval (< 450 msec, 450-480 msec, 481-500 msec, and ≥ 500msec) will be summarized at baseline and each of the subsequent time points. Categories of changes from baseline (≥ 30 msec and ≥ 60 msec) will be summarized as well.

Maximum QTc intervals and maximum changes from baseline will also be summarized similarly in a separate display.

ECG abnormalities will be presented in a data listing.

5.11.4 Vital Signs

The actual values of vital sign parameters including temperature, blood pressure, heart rate, respiratory rate, and body weight, will be summarized over time for each treatment arm. Change from baseline will also be presented.

A by-patient listing will also be presented.

5.11.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

Eastern Cooperative Oncology Group performance status and change from baseline will be summarized. Shifts from baseline to the worst post-baseline score will be tabulated by treatment arm.

5.11.6 Other Safety Assessments

Pregnancy testing results will be presented in a by-patient listing.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN9708, e.g. analyses of TEAEs of clinical importance. Tables will be provided with a summary of the patient incidence of all TEAEs of clinical importance by PT, severity, and seriousness for each analysis set within each category of TEAEs of clinical importance.

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Reference materials for this statistical plan include Clinical Study Protocol C16014 (Protocol Amendment 3 dated 10 May 2017).

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.1 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Patient populations are defined in Section 2.

Baseline values are defined in Section 5.4.2.

8. APPENDIX

8.1 Proof of Strong Control of Type I Error Rate

Proof of strong control of Type I error rate for testing PFS and OS in ITT and PFS in subgroups:

With the proposed testing procedure for the PFS testing in ITT population and three subgroups and OS testing in ITT population, this is to prove the strong control of overall Type I error rate at one-sided 0.025 level. All alpha specified in the proof is one-sided.

We will first prove the strong control of Type I error rate under the original plan without sample size re-estimation for OS. The proof can be easily generalized to incorporate the OS sample size adaptation by switching the regular logrank test statistics at final analysis with the CHW test statistic. All the equations related to OS ITT testing still hold because the join multivariate distribution of log-rank test statistics at IA1, IA2 and FA based on planned design is the same as the log-rank test statistics at IA1, IA2, and CHW test statistic at FA.

To facilitate the probability presentation, we introduce the following notations. Let the family of null hypotheses of interest be:

- $H_0^{PFS}: S_1^{PFS}(t) = S_0^{PFS}(t)$ (no difference in PFS ITT between treatment and control arm)
- $H_0^{PFS_1}: S_{S_1,1}^{PFS}(t) = S_{S_1,0}^{PFS}(t)$ (no difference in PFS subgroup 1 between treatment and control)
- $H_0^{PFS_2}: S_{S_2,1}^{PFS}(t) = S_{S_2,0}^{PFS}(t)$ (no difference in PFS subgroup 2 between treatment and control)
- $H_0^{PFS_3}: S_{S_3,1}^{PFS}(t) = S_{S_3,0}^{PFS}(t)$ (no difference in PFS subgroup 3 between treatment and control)
- $H_0^{OS}: S_1^{OS}(t) = S_0^{OS}(t)$ (no difference in OS ITT between treatment and control arm)

Let T_1^P, T_2^P (and p_1^P, p_2^P) denote the ITT PFS logrank test statistic (and corresponding p-values) at IA1 and IA2; T_1^O, T_2^O, T_3^O (and p_1^O, p_2^O, p_3^O) denote the ITT OS logrank test statistic (and corresponding p-values) at IA1, IA2, and FA; T_{S1}, T_{S2}, T_{S3} (and p_{S1}, p_{S2}, p_{S3}) denote the PFS logrank test statistic (and corresponding p-values) at IA2 for subgroup 1, 2 and 3. Also let $p_{S(1)}$, $p_{S(2)}$, $p_{S(3)}$ denote the ordered p-values among the three subgroups; $p_{S(1)}^{\{1,2\}}$, $p_{S(2)}^{\{1,2\}}$ denote the ordered p-values among subgroup 1, and 2; $p_{S(1)}^{\{1,3\}}$, $p_{S(2)}^{\{1,3\}}$ denote the ordered p-values among subgroup 1, and 3; $p_{S(1)}^{\{2,3\}}$, $p_{S(2)}^{\{2,3\}}$ denote the ordered p-values among

subgroup 2, and 3. Let c_1, c_2 be the critical value for PFS ITT testing based on O'Brien Fleming alpha spending function where $P\{p_1^P < c_1 \text{ or } p_2^P < c_2\}$=0.02 under H_0^{PFS}; d_1, d_2, d_3 be the critical value for OS ITT testing based on O'Brien Fleming alpha spending function where $P\{p_1^O < d_1 \text{ or } p_2^O < d_2 \text{ or } p_3^O < d_3\} = 0.02$ under H_0^{OS}; d_3^* be the new critical value for OS ITT testing at FA where d_3^* is calculated such that $P\{p_1^O \geq d_1, p_2^O \geq d_2, p_3^O < d_3^*\}$=0.025 - $P\{p_1^O < d_1 \text{ or } p_2^O < d_2\}$ under H_0^{OS}.

Since the key secondary endpoint - OS in ITT population is not of interest unless efficacy in the primary endpoint - PFS in ITT population is shown, there are defined paths to decision making. Liu and Hsu (2006) [6] outlined a decision path principle stating that null hypotheses should be formulated so that decision making naturally follows logical paths. We will follow this principle in formulating the null hypotheses in this proof. As a result, instead of testing all 2^5-1=31 intersection hypotheses by closed testing, we only need to test (2+1)*(2^3)-1=23 hypotheses as listed in Table 1.

Table 1: Partition hypotheses following decision paths for the proposed testing procedure

Index	Partition Hypothesis	Rejection Rule
1	$H_0^{PFS} \cap H_0^{PFS_1} \cap H_0^{PFS_2} \cap H_0^{PFS_3}$	$\{p_1^P < c_1 \text{or } p_2^P < c_2\}$ or $\{ p_{S(1)} < \frac{0.005}{3}$ or $p_{S(2)} < \frac{0.005}{2}$ or $p_{S(3)} < 0.005\}$
2	$H_0^{PFS} \cap H_0^{PFS_1} \cap H_0^{PFS_2} \cap (H_0^{PFS_3})^c$	$\{p_1^P < c_1 \text{or } p_2^P < c_2\}$ or $\{ p_{S(1)}^{\{1,2\}} < \frac{0.005}{2}$ or $p_{S(2)}^{\{1,2\}} < 0.005\}$
3	$H_0^{PFS} \cap H_0^{PFS_1} \cap (H_0^{PFS_2})^c \cap H_0^{PFS_3}$	$\{p_1^P < c_1 \text{or } p_2^P < c_2\}$ or $\{ p_{S(1)}^{\{1,3\}} < \frac{0.005}{2}$ or $p_{S(2)}^{\{1,3\}} < 0.005\}$
4	$H_0^{PFS} \cap H_0^{PFS_1} \cap (H_0^{PFS_2})^c \cap (H_0^{PFS_3})^c$	$\{p_1^P < c_1 \text{or } p_2^P < c_2\}$ or $\{ p_{S1} < 0.005\}$
5	$H_0^{PFS} \cap (H_0^{PFS_1})^c \cap H_0^{PFS_2} \cap H_0^{PFS_3}$	$\{p_1^P < c_1 \text{or } p_2^P < c_2\}$ or $\{ p_{S(1)}^{\{2,3\}} < \frac{0.005}{2}$ or $p_{S(2)}^{\{2,3\}} < 0.005\}$
6	$H_0^{PFS} \cap (H_0^{PFS_1})^c \cap H_0^{PFS_2} \cap (H_0^{PFS_3})^c$	$\{p_1^P < c_1 \text{ or } p_2^P < c_2\}$ or $\{ p_{S2} < 0.005\}$
7	$H_0^{PFS} \cap (H_0^{PFS_1})^c \cap (H_0^{PFS_2})^c \cap H_0^{PFS_3}$	$\{p_1^P < c_1 \text{ or } p_2^P < c_2\}$ or $\{ p_{S3} < 0.005\}$
8	$H_0^{PFS} \cap (H_0^{PFS_1})^c \cap (H_0^{PFS_2})^c \cap (H_0^{PFS_3})^c$	$\{p_1^P < c_1 \text{ or } p_2^P < c_2\}$
9	$(H_0^{PFS})^c \cap H_0^{OS} \cap H_0^{PFS_1} \cap H_0^{PFS_2} \cap H_0^{PFS_3}$	$\{p_1^O < d_1 \text{ or } p_2^O < d_2 \text{ or } p_3^O < d_3\}$ or $\{ p_{S(1)} < \frac{0.005}{3}$ or $p_{S(2)} < \frac{0.005}{2}$ or $p_{S(3)} < 0.005\}$

10	$(H_0^{PFS})^c \cap H_0^{OS} \cap H_0^{PFS_1} \cap H_0^{PFS_2} \cap (H_0^{PFS_3})^c$	$\{p_1^O < d_1 \text{ or } p_2^O < d_2 \text{ or } p_3^O < d_3\}$ or $\{ p_{S(1)}^{\{1,2\}} < \frac{0.005}{2} \text{ or } p_{S(2)}^{\{1,2\}} < 0.005\}$
11	$(H_0^{PFS})^c \cap H_0^{OS} \cap H_0^{PFS_1} \cap (H_0^{PFS_2})^c \cap H_0^{PFS_3}$	$\{p_1^O < d_1 \text{ or } p_2^O < d_2 \text{ or } p_3^O < d_3\}$ or $\{ p_{S(1)}^{\{1,3\}} < \frac{0.005}{2} \text{ or } p_{S(2)}^{\{1,3\}} < 0.005\}$
12	$(H_0^{PFS})^c \cap H_0^{OS} \cap H_0^{PFS_1} \cap (H_0^{PFS_2})^c \cap (H_0^{PFS_3})^c$	$\{p_1^O < d_1 \text{ or } p_2^O < d_2 \text{ or } p_3^O < d_3\}$ or $\{ p_{S1} < 0.005\}$
13	$(H_0^{PFS})^c \cap H_0^{OS} \cap (H_0^{PFS_1})^c \cap H_0^{PFS_2} \cap H_0^{PFS_3}$	$\{p_1^O < d_1 \text{ or } p_2^O < d_2 \text{ or } p_3^O < d_3\}$ or $\{ p_{S(1)}^{\{2,3\}} < \frac{0.005}{2} \text{ or } p_{S(2)}^{\{2,3\}} < 0.005\}$
14	$(H_0^{PFS})^c \cap H_0^{OS} \cap (H_0^{PFS_1})^c \cap H_0^{PFS_2} \cap (H_0^{PFS_3})^c$	$\{p_1^O < d_1 \text{ or } p_2^O < d_2 \text{ or } p_3^O < d_3\}$ or $\{ p_{S2} < 0.005\}$
15	$(H_0^{PFS})^c \cap H_0^{OS} \cap (H_0^{PFS_1})^c \cap (H_0^{PFS_2})^c \cap H_0^{PFS_3}$	$\{p_1^O < d_1 \text{ or } p_2^O < d_2 \text{ or } p_3^O < d_3\}$ or $\{ p_{S3} < 0.005\}$
16	$(H_0^{PFS})^c \cap H_0^{OS} \cap (H_0^{PFS_1})^c \cap (H_0^{PFS_2})^c \cap (H_0^{PFS_3})^c$	$p_1^O < d_1$ or $p_2^O < d_2$ or $p_3^O < d_3^*$
17	$(H_0^{PFS})^c \cap (H_0^{OS})^c \cap H_0^{PFS_1} \cap H_0^{PFS_2} \cap H_0^{PFS_3}$	$p_{S(1)} < \frac{0.005}{3}$ or $p_{S(2)} < \frac{0.005}{2}$ or $p_{S(3)} < 0.005$
18	$(H_0^{PFS})^c \cap (H_0^{OS})^c \cap H_0^{PFS_1} \cap H_0^{PFS_2} \cap (H_0^{PFS_3})^c$	$p_{S(1)}^{\{1,2\}} < \frac{0.005}{2}$ or $p_{S(2)}^{\{1,2\}} < 0.005$
19	$(H_0^{PFS})^c \cap (H_0^{OS})^c \cap H_0^{PFS_1} \cap (H_0^{PFS_2})^c \cap H_0^{PFS_3}$	$p_{S(1)}^{\{1,3\}} < \frac{0.005}{2}$ or $p_{S(2)}^{\{1,3\}} < 0.005$
20	$(H_0^{PFS})^c \cap (H_0^{OS})^c \cap H_0^{PFS_1} \cap (H_0^{PFS_2})^c \cap (H_0^{PFS_3})^c$	$p_{S1} < 0.005$
21	$(H_0^{PFS})^c \cap (H_0^{OS})^c \cap (H_0^{PFS_1})^c \cap H_0^{PFS_2} \cap H_0^{PFS_3}$	$p_{S(1)}^{\{2,3\}} < \frac{0.005}{2}$ or $p_{S(2)}^{\{2,3\}} < 0.005$
22	$(H_0^{PFS})^c \cap (H_0^{OS})^c \cap (H_0^{PFS_1})^c \cap H_0^{PFS_2} \cap (H_0^{PFS_3})^c$	$p_{S2} < 0.005$
23	$(H_0^{PFS})^c \cap (H_0^{OS})^c \cap (H_0^{PFS_1})^c \cap (H_0^{PFS_2})^c \cap H_0^{PFS_3}$	$p_{S3} < 0.005$

By partition principle, as long as each of the disjoint partition hypothesis is tested at level 0.025, the overall Type I error rate is also strongly controlled at the same level.

For hypotheses 17-23, Huang and Hsu (2007) [7] showed that the rejection rule in Table 1 is equivalent to the Hochberg procedure with overall 0.005 for testing the three subgroups.

For hypothesis 1, using Bonferroni inequality, the probability of false rejection is no greater than $P\{p_1^P < c_1 \text{ or } p_2^P < c_2\} + P\{ p_{S(1)} < \frac{0.005}{3} \text{ or } p_{S(2)} < \frac{0.005}{2} \text{ or } p_{S(3)} <$

0.005}=0.02+0.005=0.025. Similarly, for hypotheses 2-7, using Bonferroni inequality easily shows that the probability of false rejection is no greater than 0.02+0.005=0.025.

For hypothesis 8, P{$p_1^P < c_1$ or $p_2^P < c_2$}=0.02<0.025.

For hypothesis 9, using Bonferroni inequality, the probability of false rejection is no greater than P{$p_1^O < d_1$ or $p_2^O < d_2$ or $p_3^O < d_3$} + P{ $p_{S(1)} < \frac{0.005}{3}$ or $p_{S(2)} < \frac{0.005}{2}$ or $p_{S(3)} < 0.005$}=0.02+0.005=0.025. Similarly, for hypotheses 10-15, using Bonferroni inequality easily shows that the probability of false rejection is no greater than 0.02+0.005=0.025.
For hypothesis 16, P{$p_1^O < d_1$ or $p_2^O < d_2$ or $p_3^O < d_3^*$}= P{$p_1^O < d_1$ or $p_2^O < d_2$} + P{$p_1^O \geq d_1, p_2^O \geq d_2, p_3^O < d_3^*$}+ =0.025.

Since each partition hypothesis in Table 1, is tested at 0.025 level, the overall Type I error rate is also controlled at the 0.025 level.

Next is to see that after collating results from the rejection rules in Table 1, it is equivalent to the proposed testing procedure. In order to reject H_0^{PFS}, all of partition hypotheses 1-8 have to be rejected (since they involve the null space of H_0^{PFS}) which means {$p_1^P < c_1$ or $p_2^P < c_2$} which corresponds to the group sequential testing of PFS in ITT population. In order to reject $H_0^{PFS_1}$, hypotheses 1-4, 9-12, 17-20 have to be rejected which is the same as requiring hypothesis 17-20 be rejected. Similarly, hypothesis 17, 18, 21, 22 are required to be rejected for $H_0^{PFS_2}$ and hypotheses 17, 19, 21, 23 are required to be rejected for $H_0^{PFS_3}$. All the involved hypotheses are 17-23 and based on Huang and Hsu (2007), the testing procedure is exactly the Hochberg procedure with overall alpha of 0.005 level. In order to reject H_0^{OS}, all of partition hypotheses 1-16 have to be rejected. This means PFS in ITT population has to be rejected first (hypotheses 1-8). Then either {$p_1^O < d_1$ or $p_2^O < d_2$ or $p_3^O < d_3$} when $p_{S(3)} \geq 0.005$; or {$p_1^O < d_1$ or $p_2^O < d_2$ or $p_3^O < d_3^*$} when $p_{S(3)} < 0.005$ has to hold. This means OS in ITT population can either be rejected at first IA based on d_1 (given PFS in ITT is rejected first) or second IA based on d_2 (given PFS in ITT is rejected); if not, depending on whether all three subgroups at second IA can be rejected or not, OS in ITT population can be tested again at final analysis based on either d_3 or d_3*.

For the other two key secondary endpoints, CR rate will be tested at the same alpha level, instead of same critical value, as that for OS whenever OS reaches statistical significance. Pain response rate will be tested at the same alpha level as that for CR rate whenever CR

rate reaches statistical significance. Due to the closed sequential testing property, the family-wise error rate is strongly controlled for both the primary endpoint and three key secondary endpoints.

8.2 **Calculating the Significance Boundary for ITT PFS at IA2**

All alpha specified in this section is one-sided.

In the previous SAP (SAP version 1), the significance boundaries c_1 and c_2 for ITT PFS at IA1 and IA2 were to be calculated based on the Gamma(-1) alpha-spending approach. Specifically, c_1 was to be calculated using the observed number of PFS events at IA1 and in anticipation of 435 PFS events at IA2. c_2 was to be calculated with the purpose of exhausting the remaining available alpha while considering the correlation between c_1 and the observed number of PFS events at IA2.

This SAP (SAP version 2) modifies the target number of PFS events at IA2 from approximately 435 to approximately 370. It is also proposed after the Sponsor observed an aggregate 328 PFS events at IA1, while remaining blinded to any data by treatment arm. Therefore, to preserve the type I error rate, the significance boundary for ITT PFS at IA2 (the FA for ITT PFS) will be re-calculated while the boundary at the past IA will remain unchanged. What follows is an example calculation for the situation that exactly 370 PFS events are observed at IA2. Note that the actual value of c_2 will vary slightly depending on the eventual observed number of events.

Given 328 PFS events observed at IA1, 435 PFS events planned at IA2, and the Gamma(-1) alpha-spending function, the one-sided significance cutoffs for the log-rank test statistic T_1 and p-value p_1 at IA1 are given by u_1=2.223 and c_1=0.0131, respectively. Now suppose IA2 is performed after 370 PFS events are observed instead of the planned 435. Because the correlation between the log-rank test statistic T_2 at IA2 and T_1 changes as a result, the information fraction I at IA1 should be adjusted to exhaust the remaining alpha while preserving the type I error rate.

Set I=328/370 and keep u_1=2.223. That is, update the information rate at IA1, but fix the alpha already spent at IA1. Under the null hypothesis of no treatment benefit, the vector (T_1, T_2) follows the bivariate normal distribution

$$\begin{pmatrix} T_1 \\ T_2 \end{pmatrix} \sim MVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \sqrt{I} \\ \sqrt{I} & 1 \end{pmatrix} \right)$$

By performing a grid search, it can be found that setting u_2=2.131 preserves type I error rate at alpha-level 0.02:

$$\Pr(T_1 > u_1) + \Pr(T_1 < u_1 \text{ and } T_2 > u_2) = 0.02$$

The p-value cutoff corresponding to u_2 is c_2=0.0165.

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ELECTRONIC SIGNATURES

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CCI	Pharmacovigilance Approval	14-Jan-2020 19:52 UTC
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	Clinical Approval	14-Jan-2020 19:56 UTC
	Biostatistics Approval	15-Jan-2020 14:39 UTC