CLINICAL STUDY PROTOCOL

X16035

A Phase II Trial of Nonmyeloablative Haploidentical Peripheral Blood Stem Cell Transplantation Followed By Maintenance Therapy With the Novel Oral Proteasome Inhibitor, MLN9708, in Patients with High-risk Hematologic Malignancies

Indication:	High Risk Hematologic Malignancies
Phase:	Phase II

Protocol History

Original	07 February 2014
Amendment	22April 2014
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This is an investigator-initiated study. The principal investigator Scott R. Solomon, MD, (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

Study Title: A Phase II Trial of Nonmyeloablative Haploidentical Peripheral Blood Stem Cell Transplantation Followed By Maintenance Therapy With the Novel Oral Proteasome Inhibitor, MLN9708, in Patients with High-risk Hematologic Malignancies

Phase: II

Number of Patients: 25

Study Objectives

Primary

- To estimate the incidence of relapse/progression at one-year post-transplant.

Secondary

- To obtain estimates of overall survival (OS), event-free survival (EFS), non-relapse mortality (NRM), engraftment, acute and chronic graft-versus-host disease (GVHD).
- Characterize additional hematologic and non-hematologic toxicities of MLN9078 when given post haploidentical transplant.
- Characterize donor hematopoietic chimerism in peripheral blood at days ~30, ~60, and ~90 after HSCT.

Overview of Study Design:

In an attempt to reduce relapse risk and improve outcomes following haploidentical transplantation for patients with high risk hematologic malignancies, we will implement several strategies to augment the well documented effect of NK cell alloreactivity seen in HLA-mismatched transplantation. These strategies include (1) choosing potential haploidentical donors for optimal NK-alloreactivity, (2) utilizing proteasome inhibition post-transplant with MLN9708 to both sensitize tumor cells to NK cytotoxicity and protect against graft-versus-host disease (GVHD), and (3) eliminating mycophenolate mofetil from the post-transplant immunosuppression regimen to improve NK cell reconstitution following haploidentical peripheral blood stem cell transplantation.

Patients will receive a nonmyeloablative haploidentical transplant using a T-cell replete allograft and post-transplant cyclophosphamide as previously described at our center (Bashey et al. J Clin Oncol. 2013; 31(10):1310-6). MLN9708 will be administered once weekly for 3 weeks on a 28 day cycle for one-year post-transplant. Post-transplant immunosuppression will consist of tacrolimus only (MLN9708 will substitute for mycophenolate mofetil as the second GVHD prophylactic medication).

The primary endpoint of this trial will be the risk of relapse and/or progression at one-year post-transplant. Experience from the literature suggests that following a nonmyeloablative haploidentical transplant using post-transplant cyclophosphamide (haplo-pCy), the risk of relapse is approximately 50% at one year post-transplant. It is hoped that under this protocol, this rate will be at most 25%. Thus we statistically formalize this study by testing the null hypothesis that p, the PFS rate is 0.25 or less versus the alternative hypothesis that p is greater than 0.5. A sample size of 25 patients gives 90% power with an alpha=0.05, using the formula for a one sample binomial (two-sided) test of a proportion.

Correlative samples will be drawn at baseline, day 30, 60, 90, 6mo, 12 months for lymphocyte subsets. Additional PBMCs will be collected and frozen for future immune reconstitution studies. Approximately 30-50ml of blood will be collected at each time point.
Study Population: Eligible patients will be at least 18 years of age, with adequate performance status and organ function, and have a high risk hematologic malignancy (acute lymphoblastic leukemia/lymphoma in complete remission, acute myeloid leukemia in complete remission, relapsed Burkitt leukemia/lymphoma in complete remission, multiple myeloma (relapsed disease and/or presence of del17p), relapsed lymphoma including marginal zone, follicular, and chemotherapy-sensitive diffuse large B cell, T cell, Mantle cell, and Hodgkin's. Full details of disease inclusion is located in section 5.1. Key Exclusion Criteria will be poor performance status, inadequate organ function, or lack of suitable haploidentical donor.
Duration of Study: # months from FPI to LPI: 24 months # months from LPI to LPO: 12 months. # months to complete study: 36 months

STUDY OVERVIEW

Days –6, -5 Fludarabine 30 mg/M^2 IV qd
Cyclophosphamide (CTX) 14.5 mg/kg IV qd

↓

Days –4→ -2 Fludarabine 30 mg/M^2 IV qd

↓

Day –1 TBI 200 cGy

↓

Day 0 Infuse unmanipulated PBSCs

↓

Days 3, 4 CTX 50 mg/kg IV q d
(hydration/Mesna)
(First dose of cyclophosphamide must be administered 48-72 hr after infusion of PBCs)

↓

Day 5 Begin Tacrolimus and
MLN9708 4mg weekly x 3doses q28days, up to 12 monthly cycles

↓

Day 30, 60, 90 Assess Chimerism in peripheral blood

↓

Day 180 Discontinue Tacrolimus

SCHEDULE OF EVENTS

Test	Screen	Month 1 (4 weekly visits)	Month 2 (4 weekly visit)	Month 3 (4 weekly visits)	Month 4	Month 5	Month 6	Months 7-11	Month 12	End of Study	Months 18, 24 and 36
H & P	X	X	X	X	X	X	X	X	X	X	X
CBC with differential	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X
PFT*	X										
ECHO*	X										
EKG*	X										
IDMs including Hepatitis & HIV*	X										
Pregnancy test **(FOCBP)	X										
GVHD assessment		X	X	X	X	X	X	X	X	X	X
Toxicity Assessment		X	X	X	X	X	X	X	X	X	X
Bone marrow biopsy & aspirate				X			X		X	X	X
CT/PET for NHL/HD for disease assessment				X			X		X	X	X
Research Sample***	X	X (Day 30)	X (Day 60)	X (Day 90)			X		X		
Survival											X
New malignancy assessment											X

*Testing that is done for transplant is acceptable if done within 6 weeks of the start of study drug.
**Women with a uterus <50 or women >50 but < one year without a menstrual cycle) are considered

FOCBP.

*** Research samples will be collected for lymphocyte subsets. Additional PBMCs will be collected to be frozen for future immune reconstitution studies. Approximately 30-50ml of blood will be collected at each time point.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
Ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	Benzodiazepines
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
CNS	central nervous system

Abbreviation	Term
CO_2	carbon dioxide
CR	complete remission
CRM	continual reassessment method
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	cardiovascular
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose

Abbreviation	Term
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial remission
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	*quaque die*; each day; once daily

Abbreviation	Term
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
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
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

Allogeneic HSCT is a potentially curative treatment for a variety of hematologic malignancies and non-malignant hematologic disorders[1]. Of all the potential sources of allografts, HSCT from a HLA-matched sibling has generally produced the best overall outcomes[2]. Unfortunately, only about a third of candidates for HSCT have HLA-matched siblings. For patients who lack HLA-matched siblings, there are three alternative sources of stem cells for HSCT: 1) volunteer unrelated donors; 2) umbilical cord blood; and 3) partially HLA-matched, or haploidentical, related donors[3]. Since any patient shares exactly one HLA haplotype with each biological parent or child and half of siblings, an eligible haploidentical donor can be identified rapidly in nearly all cases. However, haploidentical HSCT has been associated with significant risks of graft rejection and severe GVHD[4-6], which are manifestations of excessive alloreactivity by host[7] and donor T cells[8], respectively. The risk of severe GVHD may be reduced in intensively conditioned recipients of grafts that have been rigorously depleted of T cells, but the risks of serious infection and death from prolonged immune compromise in these patients remains high[9-14]. Mortality from CMV disease was 14% in a recent study of nonmyeloablative transplantation using HLA-haploidentical donors[15]. Fukuda, et al. reported an incidence of 15% invasive mold infections in nonmyeloablative transplants from HLA-matched related or unrelated donors with a mortality rate of 56%[16]. In order to reduce the toxicity of haploidentical HSCT, methods to selectively inhibit alloreactivity while preserving immunity to infection and the malignancy are clearly required[17].

Cyclophosphamide (Cy) is a highly immunosuppressive antineoplastic agent that has an established role in conditioning for HSCT. Typically, the drug is administered prior to transplantation to prevent graft rejection by suppressing the host immune system. However, pre-transplantation conditioning with Cy increases the risk of GVHD following allogeneic T cell infusion in mouse models[18]. In contrast, administration of a properly timed, high dose of Cy *after* HSCT inhibits both graft rejection and GVHD[19-22].

Based on these murine studies, investigators at Johns Hopkins University developed a non-myeloablative conditioning regimen for transplantation of non-T cell-depleted marrow from partially HLA-matched, or haploidentical, bone marrow from first-degree relatives[23]. This study demonstrated the optimal titration of post-transplantation Cy dose, given in conjunction with pre-transplantation fludarabine and total body irradiation (TBI), to achieve a regimen that had an acceptably low risk of graft rejection and GVHD, the two major complications of haploidentical

HSCT. All patients received mycophenolate mofetil (MMF) and tacrolimus, beginning 24 hours after post-transplant Cy administration for GVHD prophylaxis. A total of 88 patients with poor risk hematologic malignancies were studied. The median times to neutrophil and platelet recovery for all patients were 15 and 24 days, respectively. Graft failure occurred in a total of 15/84 patients (18%). All but two patients with graft failure experienced recovery of autologous hematopoiesis with median times to neutrophil and platelet engraftment of 24 days (range 11-48 days) and 44 days (range 15-395 days), respectively.

The cumulative incidences of grades II-IV and III-IV acute GVHD by day 200 were 35% and 10%. The cumulative incidence of chronic and extensive chronic GVHD in the first year after transplantation for the entire population was 22% and 14%, respectively. The cumulative incidences of NRM at 180 days and 1 year after transplantation were 13% and 19%, respectively. The cumulative incidences of relapse at 1 and 2 years after transplantation were 50% and 57%, respectively. At a median follow-up of survivors of 817 days (range, 112-1808 days), the actuarial overall survival at 1 and 2 years were 45% and 35%, respectively. The actuarial EFS at 1 and 2 years were 32% and 24%, respectively. Furthermore, CMV reactivation was observed in 20 of 60 (33%) high-risk patients, and proven or probable invasive mold infections post-transplant, all caused by *Aspergillus sp*, were observed in 6 of 88 (6.8%) patients, of whom two had infection prior to transplant. Two patients died from *Aspergillus* infection, one while persistently neutropenic following graft failure. There was no CMV-associated mortality.

From these results, it was concluded that (1) post-transplantation immunosuppression with high dose Cy, tacrolimus, and MMF was associated with an acceptably low incidence of graft rejection, severe acute GVHD, and extensive chronic GVHD, (2) there was effective clinical immune reconstitution as demonstrated by the low incidence of severe opportunistic infections, and (3) relapse represented the major cause of treatment failure. Strategies to decrease the relapse risk are clearly needed.

Clinical data from haploidentical transplantation (haplo-HSCT) has revealed that NK cells are responsible for remarkably favorable effects in adults with AML and more recently, in children with high-risk ALL[24-27]. The emergence of the concept of NK cell alloreactivity has represented an important advance in the field of haplo-HSCT, underlining for the first time that not only adaptive immunity, but also innate immunity is a crucial element for a successful clinical outcome. Indeed, it has become evident that the therapeutic effect of haplo-HSCT is in part dependent on the graft-versus-leukemia (GVL) effect exerted by NK cells which originate from the donor allograft.

Each NK cell expresses one or more inhibitory receptors (KIR), which through interactions with self-HLA class I molecules, prevent NK cell-mediated attack against healthy, autologous cells. On the other hand, cells in which HLA class I expression is compromised (for example, after tumor transformation or viral infection) become susceptible to NK-mediated killing. Thus, in an autologous setting, NK cells can kill only cells that do not express sufficient HLA class I molecules, whereas in a nonself environment, NK cells may kill allogeneic cells when they express inhibitory KIRs that are not engaged by any of the HLA class I alleles present on allogeneic target cells. As a NK-mediated, alloreactive response depends on the failure of KIRs to engage their HLA class I ligands, alloreactive NK cells have been said to see "missing self" on allogeneic target cells. Alloreactivity in haplo-HSCT is operating through the mechanism of missing-self recognition, provided that the donor expresses a KIR ligand that is missing in the recipient's HLA genotype and expresses the specific inhibitory KIR, leading to a KIR/KIR ligand mismatch in the donor-versus-recipient direction.

A number of activating forms of KIRs (e.g., KIR2DS1, KIR2DS2, and KIR3DS1) have been recently described, which are highly homologous in the extracellular domain to their inhibitory counterparts and present a short cytoplasmic tail lacking ITIM (immunoreceptor tyrosine-based inhibition motifs) . Inhibitory/activating KIRs as well as HLA are two polymorphic gene systems. As they are encoded on separate chromosomes, they segregate independently. Over 350 different KIR genotypes have been described, which highlights the great variability in the KIR gene family. Combinations of HLA class I and KIR variants influence resistance to infections, susceptibility to autoimmune diseases, and complications of pregnancy, as well as outcome after hematopoietic stem cell transplantation. All HLA/KIR combinations can be divided in two basic KIR haplotypes: group A haplotypes, which have a fixed number of genes that encode inhibitory receptors (with the exception of the activating receptor KIR2DS4), and group B haplotypes, which have variable gene contents, including additional activating receptor genes. Recent studies have suggested that donor group B haplotypes yield significantly better protection against leukemic relapses, as compared with group A, and improved disease-free survival in patients undergoing T cell-depleted HSCT for AML[28-30].

Research has shown that NK cell cytotoxicity can be potentiated in vitro by pre-exposing tumor cells to the proteasome inhibitor, Bortezomib[31]. Pretreatment of tumor cells with Bortezomib has been shown to increase NK-mediated tumor control in multiple cancer types including myeloma, leukemia, renal cell carcinoma, prostate cancer, breast cancer, squamous cell and hepatocellular carcinoma[32-37]. Enhanced NK cell killing effect is in part dependent on the up-regulation of receptors on the tumor surface for tumor necrosis factor related apoptosis inducing ligand (TRAIL) and to drug-induced augmentation of tumor caspase-8 activity, leading to

enhanced tumor killing via perforin/granzyme mediated NK-tumor cytotoxicity[32]. Other mechanisms of action include down-regulation of class I HLA on tumor cells[34], as well as selectively induced the expression of the tumor cells NKG2D ligands, MICA and MICB[33,38].

In animal models, systemic proteasome inhibition has been shown to significantly inhibit acute GVHD while preserving graft-versus-tumor (GVT) responses in advanced tumor-bearing mice after allogeneic BMT with no observed adverse effects on myeloid recovery and donor chimerism[39]. Bortezomib has been shown to decrease T-helper 1 responses among alloreactive T-lymphocytes[40], while preserving regulatory T cells[41,42] and T cell responses against pathogens[43]. Clinical studies utilizing a short course of bortezomib with tacrolimus/methotrexate for GVHD prophylaxis demonstrated low rates of GVHD in HLA-mismatched unrelated donor transplants, while improving T cell and NK cell reconstitution[44].

It is therefore hypothesized that proteasome inhibition can improve the results of haploidentical transplantation by both preventing GVHD and augmenting GVT through its enhancement of alloreactive NK cell function. MLN9708 is a selective, orally bioavailable, second-generation proteasome inhibitor, which has a shorter proteasome dissociation half-life and improved pharmacokinetics, pharmacodynamics, and antitumor activity compared with bortezomib. In clinical studies of patients with myleoma, MLN9708 has shown comparable clinical activity and a better safety profile when compared to bortezomib[45]. Benefits of MLN9708 include the convenience of once weekly oral fixed dosing as well as a significantly decreased risk of peripheral neuropathy, which is one of the biggest impediment to long-term administration of bortezomib. We further hypothesize that the combination of tacrolimus and MLN9708 will provide sufficient GVHD prophylaxis making it possible to eliminate the need for mycophenolate mofetil, which has been shown to significantly decrease NK cell proliferation and cytotoxic function[46].

1.1.1 Disease Under Treatment

High risk hematologic malignancies with standard indication for nonmyeloablative haploidentical transplantation include acute lymphoblastic leukemia/lymphoma in complete remission, acute myeloid leukemia in complete remission, relapsed Burkitt leukemia/lymphoma in complete remission, multiple myeloma (relapsed disease and/or presence of del17p), relapsed lymphoma including marginal zone, follicular, and chemotherapy-sensitive diffuse large B cell, T cell, Mantle cell, and Hodgkin's. Specific disease criteria are listed in section 5.1 Inclusion Criteria.

1.1.2 MLN9708

1.2 Preclinical Experience

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

1.3 Clinical Experience

As of 30 April 2012, 382 patients have been treated with MLN9708 across 9 enrolling, sponsor-led phase 1 or phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. MLN9708 is available as an intravenous and oral formulation. Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral MLN9708 has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a different yet related plasma cell dyscrasia, systemic light chain (AL) amyloidosis. A clinical pharmacology study looking at drug-drug interactions (DDIs), the effect of food, and bioavailability also uses the oral formulation. Details of these trials can be found in ClinicalTrials.gov and the MLN9708 IB.

1.4 Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to first maximum plasma concentration (T_{max}) of approximately 0.5 to 2.0 hours and terminal $t_{1/2}$ after multiple dosing of approximately 5 to 7 days[47]. 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[48]. Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. See the IB for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human

CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

1.5 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 or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-1.

Table 1-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 58	PO, twice weekly (TW), single agent	0.24-2.23 mg/m^2, TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia
C16004 RRMM N = 52	PO, weekly (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*: 4.0 mg fixed (switched to fixed dosing in phase 2, relevant to 2.23 mg/m^2)
C16006 NDMM N = 28	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with melphalan and prednisone	Arm A*: 3-3.7 mg, fixed dose, TW DLT: rash, thrombocytopenia, subileus Arm B*: 5.5 mg, fixed dose, W DLT: Esophageal ulcer
C16007 RRAL N = 6	PO, W, single agent	4-5.5 mg, fixed dose*, W MTD: 4 mg DLT: thrombocytopenia, dirrhea, 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* W MTD: 4 mg
C16009 Solid tumors, Lymphomas N = 22	PO, W, single agent	5.5 mg fixed dose* W
C16010 RRMM N = 1	PO, W, combination with LenDex	4.0 mg fixed dose* W
TB-MC010034 RRMM N = 5	PO, W, single agent in 1s part of study then in combination with LenDex in 2nd part	3.0 mg fixed dose* W DLT: thrombocytopenia, nausea, hypertension, diarrhea

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

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

Overview of the Oral Formulation of MLN9708

The emerging safety profile indicates that oral MLN9708 is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care. From experience from phase 1 through 2 studies the major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 24 months.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 146 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral MLN9708 Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-2 Summary of Most Common (At Least 10% of Total) All Grade Treatment-Emergent Adverse Events (Oral MLN9708 Single-Agent [C16003/4/7/9] Safety Population)

Primary System Organ Class	Preferred Term and Incidence N=146 n (%)
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 102 (70)	Nausea 68 (47); Diarrhoea 55 (38); Vomiting 51 (35); Abdominal pain 21 (14); Constipation 21 (14)
General disorders and administration site conditions 98 (67)	Fatigue 71 (49); Pyrexia 31 (21); Oedema peripheral 15 (10)
Blood and lymphatic system disorders 77 (53)	Thrombocytopenia 60 (41); Anaemia 30 (21); Neutropenia 23 (16); Leukopenia 15 (10)
Nervous system disorders 63 (43)	Headache 20 (14); Dizziness 18 (12)
Metabolism and nutrition disorders 60 (41)	Decreased appetite 39 (27) Dehydration 21 (14)
Respiratory, thoracic and mediastinal disorders 60 (41)	Cough 22 (15); Dyspnoea 21 (14)
Skin and subcutaneous tissue disorders 60 (41)	Rash macular 17 (12)
Musculoskeletal and connective tissue disorders 56 (38)	Arthralgia 20 (14); Back pain 17 (12)
Infections and infestations 54 (37)	Upper respiratory tract infection 21 (14)

Source: MLN9708 Investigator's Brochure Edition 6

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator

In the 3 studies actively enrolling patients to investigate oral MLN9708 in combination with standard combination regimens in patients with newly diagnosed multiple myeloma, a total of 96 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 in combination with lenalidomide and dexamethasone in 2 trials (C16005 and C16008) and with melphalan and prednisone in 1 trial (C16006). The most frequent (at least 10%) adverse events occurring in the pooled safety population from Studies C16005, C16006, and C16008 is shown in Table 1-3. In combinations trials, related is defined as possibly related to any drug in the combination regimen, not just specifically related to MLN9708.

Table 1-3 Summary of Most Common (At Least 10% of Total) Treatment- Emergent Adverse Events (Oral MLN9708 Combination Agent [C16005/6/8] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N= 96 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 70 (73)	Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26) Diarrhoea 22 (23)
General disorders and administration site conditions 64 (67)	Fatigue 37 (39); Oedema peripheral 20 (21); Pyrexia 19 (20)
Skin and subcutaneous tissue disorders 57 (59)	Rash 13 (14)
Nervous system disorders 46 (48)	Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11)
Musculoskeletal and connective tissue disorders 45 (47)	Back pain 18 (19); Muscle spasms 10 (10)
Blood and lymphatic system disorders 42 (44)	Thrombocytopenia 28 (29); Anaemia 22 (23); Neutropenia 19 (20)
Infections and infestations 40 (42)	Upper respiratory tract infection 17 (18);
Metabolism and nutrition disorders 38 (40)	Decreased appetite 11 (11)
Respiratory, thoracic and mediastinal disorders 34 (35)	Dyspnoea 13 (14); Cough 11 (11)
Psychiatric disorders 23 (24)	Insomnia 15 (16)

Source: MLN9708 Investigator's Brochure Edition 6.

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

The clinical experience with MLN9708 also 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. The antitumor activity has been seen with single-agent MLN9708, when combined with established therapies, and across the malignancies studied (advanced solid tumors[49], non-Hodgkin's disease, Hodgkin's disease[50], relapsed and/or refractory multiple myeloma [RRMM; [51,52]], relapsed or refractory systemic light chain amyloidosis [RRAL; [53]], and newly diagnosed multiple myeloma [NDMM; [54-56]] to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of MLN9708.

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agent MLN9708 is administered weekly in patients with RRMM or RRAL, respectively.

1.6 Relapsed and/or Refractory Multiple Myeloma

Study C16004 is an open-label, dose-escalation, phase 1 study of MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. The dose-escalation phase of the trial has completed. In this study, 2 of 3 patients experienced protocol-defined DLTs (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m2. As per protocol, subsequent patients were treated at 1 dose level below (2.97mg/m2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral MLN9708 was determined to be 2.97 mg/m2.

Once the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled in order to further evaluate the safety, tolerability, efficacy, PK, and pharmacodynamics of oral MLN9708. The MTD expansion cohorts enrolling are:

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];

2. Carfilzomib expansion cohort

3. Proteasome Inhibitor-Naïve expansion cohort

4. VELCADE-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest MLN9708 has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated[57, 58].

As of the 30 April 2012 data cut, these patients are considered heavily pretreated as evidenced by a median number of 4 (range 1–13) prior lines of therapy, with 66% refractory to the last line of therapy. Patients have received a median of 2 cycles of therapy (range, 1- 11). Five patients have achieved objective response: 1 patient achieved a VGPR and 4 patients achieved a PR. Additionally, 15 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 15 patients remain on treatment; discontinuation of treatment was primarily due to progressive disease (69%).

A summary of the safety profile of patients treated in Study C16004 is outlined in Table 1-4. Overall, 92% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/ 2 in 6 patients, with 3 patients reporting baseline Grade 1 PN at study entry.

Table 1-4 Study C16004, Oral MLN9708, Single Agent, Given Weekly: Most Common TEAEs as of 30 April 12 (N= 52)

Most Common (> 20%) Any Grade and Irrespective of Cause	Thrombocytopenia (54%) Fatigue (48%) Nausea (44%), diarrhea (44%) Vomiting (37%) Decreased appetite (33%) Rash* (31%) Anemia (25%) Neutropenia (23%)
Drug-Related Grade ≥ 3 in > 5% of patients	Thrombocytopenia (38%) Diarrhea and neutropenia 17% (each), fatigue and lymphopenia 10% (each), nausea and decreased appetite 8% (each) and vomiting 6%

Source: MLN9708 Investigator's Brochure Edition 6
* Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic, pruritus,, rash erythematous, exfoliative rash, and rash popular

Dose reductions required were due to AEs that included rash, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, hypotension, increase in serum creatinine, abdominal pain, ileus, fatigue, and pneumonia. The AEs reported for the 5 patients who were required to

discontinue treatment included Grade 2 MLN9708-related nausea/vomiting in 1 patient treated above the MTD, Grade 3 MLN9708-related diarrhea in a second patient, related Grade 3 thrombocytopenia, related Grade 2 dyspnea, and not related Grade 4 elevation in creatinine (1 patient each). There were no on-study deaths.

Study C16007 is evaluating single agent weekly , Day 1, 8, and 15 of a 28-day cycle, oral dosing in patients with RRAL after at least 1 prior therapy. The objectives of this study are to determine the safety, tolerability, and MTD, as well as to determine hematologic and organ response rates in this patient population. The starting dose level was selected from Study C16004 as previously described. In Study C16007 the dose was switched from the BSA-based dosing to the fixed dose, thereby the 4.0 mg fixed starting dose in Study C16007 corresponds to the 2.23 mg/m2 dose (one dose level below MTD) from Study C16004. This study is currently enrolling patients in the dose-expansion portion of the trial.

As of 30 April 2012, 14 patients have been treated in this study. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which met the definition of a DLT due to the delay in starting Cycle 2). As per protocol, the dose was escalated to 5.5 mg for the next cohort of patients where 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram on study entry, but did have substantial renal involvement. After the occurrence of this DLT, diagnoses included cardiac involvement and CHF. The MTD of weekly oral MLN9708 was determined to be 4.0 mg. Following the establishment of the MTD, patients are currently being enrolled in to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed[59].

As of the 30 April 2012 data cut, the patients enrolled in the study are considered heavily pretreated, as evidenced by a median number of 3 prior lines of therapy (range 1–7), with 38% and 46% of patients having been previously treated with bortezomib and lenalidomide, respectively. To be eligible for the study, patients must have amyloid involvement of the heart, kidney, or both; at the data cut the organ involvement distribution was 6, 4, and 4 patients, respectively. Patients have received a median of 2.5 cycles of therapy (range, 1-12). Eight patients remain on treatment. Early signs of activity have been reported. There were 11 patients who have received at least 1 cycle of therapy with completed response assessments (9 in the 4.0 mg [MTD] cohort and 2 in the 5.5 mg cohort). The overall hematologic response rate at MTD is 56% (5 patients achieved a hematologic response [4 VGPR and 1 PR]; 3 patients showed no change, and 1 patient had an early progression.

A summary of the safety profile of patients treated in Study C16007 is outlined in Table 1-5. Overall, 86% of patients experienced a TEAE of any grade and of any cause.

Table 1-5 Study C16007, Oral MLN9708, Single Agent Given Weekly Most Common TEAEs as of 30April 12 (N = 14)

Most Common (> 20%) Any Grade and Irrespective of Cause	Nausea (50%) Fatigue (36%) Thrombocytopenia (29%) Diarrhea (29%) Decreased Appetite (21%) Peripheral Edema (21%) Dyspnea (21%) Abdominal pain (21%)
Drug-Related Grade ≥ 3 in more than 3 Patients	Thrombocytopenia 5 patients, rash 3 patients, dehydration 2 patients, fatigue 2 patients

Source: MLN9708 Investigator's Brochure Edition 6

One patient discontinued study drug administration due to a TEAE (patient with DLT of acute rise in serum creatinine, dyspnea, and cardiac arrest treated at 5.5 mg, as noted above). No death has been reported.

The potential risks reported with MLN9708 use, pooled from all studies using the oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the MLN9708 IB, SMA, and ICF documents. Regardless of whether MLN9708 is administered on the once weekly or twice weekly dosing schedule, there is consistency among the type of TEAEs reported, despite some differences in the frequency and severity of the reported events. While the predominant potential toxicities may be severe in some cases, they are largely reversible, and can be managed by routine clinical monitoring and standard medical interventions, which may include dose reductions and supportive care. Please refer to the MLN9708 IB and SMA for further information.

1.7 Newly Diagnosed Multiple Myeloma (NDMM)

In Study C16005, MLN9708 is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle. Enrollment to this study is closed.

Clinical data as of 30 April 2012 is available. The MTD in Study C16005 was determined to be 2.97 mg/m^2 given weekly in a 28-day cycle with LenDex. The DLTs were urticarial rash, dizziness, nausea, orthostatic hypotension, vomiting, diarrhoea, and syncope. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to, analyses of efficacy results and adverse events (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Given that the dose of MLN9708 at 2.97 mg/m^2 compromised the maximal dosing of lenalidomide and that the dose of 2.23 mg/m^2 is very tolerable and clinically active, Millennium designated 2.23 mg/m^2 as the RP2D after evaluation of the data and discussion with investigators. The RP2D of 2.23 mg/m^2 has been translated into a fixed dose of 4.0 mg based on the results from the population PK analysis. Enrollment in this study has been completed; 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.

In Study C16005, 15 of 15 (100%) patients in the dose escalation portion of the study experienced at least 1 TEAE irrespective of grade or causality. At the MTD across all dose expansion cohorts 49 of 53 patients (including 3 patients from the dose escalation cohort [92%]) reported at least 1 TEAE irrespective of grade or causality. In the MTD cohorts, fatigue was the most common AE reported (38%). Other common AEs reported include nausea (32%), constipation (30%), upper respiratory infection (23%), and peripheral oedema (21%). 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.

A summary of the overall safety profile of patients treated in Study C16005 is outlined in Table 1-6. Overall, 100% of 65 patients experienced at least one TEAE of any grade and of any cause.

Table 1-6 Study C16005: Oral MLN9708 Given Weekly in Combination With Lenalidomide and Dexamethasone, Most Common TEAEs as of 30 April 2012

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (37%) Nausea (34%) Constipation (31%) Vomiting (28%) Diarrhoea (26%) Thrombocytopenia (23%) Upper respiratory tract infection (22%)

Drug-Related[a] Grade ≥ 3 in ≥ 2 Patients	Anaemia and oedema peripheral (20% each) Nausea, vomiting (n=3 each) Thrombocytopenia, lymphopenia, rash pruritic (n=2 each)

Source: MLN9708 Investigator's Brochure Edition 6.

a Related means to ANY drug in the study drug combination.

The most common drug-related SAEs reported in Study C16005 as of 30 April 2012 include pneumonia, infection, diverticulitis, localised infection, gastrointestinal haemorrhage, respiratory syncytial virus (RSV) pneumonia faecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral oedma, asthenia, hyponatraemia vomiting, diarrhoea, nausea, chest pain, dehydration, anemia, dizziness, peripheral sensory neuropathy, orthostatic hypotension, embolism, muscular weakness, acute renal failure, blood creatinine increased, maculopapular rash, atrial fibrillation, syncope, hypotension, and deep vein thrombosis, and back pain.

As of the clinical data cutoff, 4 patients have discontinued treatment due to TEAEs including gastrointestinal hemorrhage, angioedema, syncope, and RSV pneumonia.

One death was reported for a patient with RSV pneumonia; the event was deemed by the investigator to be related to treatment with MLN9708.

1.8 Study Rationale

In an attempt to reduce relapse risk and improve outcomes following haploidentical transplantation for patients with high risk hematologic malignancies, we will implement several strategies to augment the well documented effect of NK cell alloreactivity seen in HLA-mismatched transplantation. These strategies include (1) choosing potential haploidentical donors for optimal NK-alloreactivity, (2) utilizing proteasome inhibition post-transplant with MLN9708 to both sensitize tumor cells to NK cytotoxicity and protect against graft-versus-host disease (GVHD), and (3) eliminating mycophenolate mofetil from the post-transplant immunosuppression regimen to improve NK cell reconstitution following haploidentical peripheral blood stem cell transplantation.

Patients will receive a nonmyeloablative haploidentical transplant using a T-cell replete allograft and post-transplant cyclophosphamide as previously described at our center (Bashey et al. J Clin Oncol. 2013; 31(10):1310-6). MLN9708 will be administered once weekly for 3 weeks on a 28 day cycle for one-year post-transplant. Post-transplant immunosuppression will consist of

tacrolimus only (MLN9708 will substitute for mycophenolate mofetil as the second GVHD prophylactic medication).

1.9 Potential Risks and Benefits

MLN9708

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

MLN9708 is a modified dipeptide boronic acid proteasome inhibitor similar to VELCADE, which has a known safety profile [VELCADE PI]. The most frequent AEs reported to date in the ongoing MLN9708 phase 1 studies were anticipated based on preclinical data and previous experience with VELCADE, and are noted in the IB, the Safety Management Attachment, and the informed consent documents. However, it is possible that MLN9708 will have toxicities that were not previously observed in or predicted from such sources. Patients will be monitored closely for anticipated toxicities.

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[49,50,51,52,54,55,56].

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

Cyclophosphamide (Cytoxan®)

Cyclophosphamide is an alkylating agent which prevents cell division primarily by cross-linking DNA strands. Cyclophosphamide is cell cycle nonspecific. Cyclophosphamide for injection is available in 500mg, 1gram, and 2000 mg vials which are reconstituted with 100 ml sterile water for injection. The concentration of the reconstituted product is 20 mg/ml. The calculated dose will be diluted further in 500-1000 ml of Dextrose 5% in water or NS. Each dose will be infused over 1-2 hr (depending on the total volume). Clinical toxicities of cyclophosphamide include alopecia, nausea and vomiting, headache and dizziness, hemorrhagic cystitis, cardiotoxicity, immunosuppression, myelosuppression, pulmonary fibrosis, increased hepatic enzymes and syndrome of inappropriate anti-diuretic hormone (SIADH).

Mesna (sodium-2-mercapto ethane sulphonate)

Mesna is a prophylactic agent used to prevent hemorrhagic cystitis induced by the oxasophosphorines (cyclophosphamide and ifosphamide). It has no intrinsic cytotoxicity and no antagonistic effects on chemotherapy. Mesna binds with acrolein, the urotoxic metabolite produced by the oxasophosphorines, to produce a non-toxic thioether and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxasophosphorines. Mesna is available in 1000 mg vials containing a 100 mg/ml solution. Mesna will be diluted and administered per institutional standards. Mesna will be utilized per standard of care for the day 3 and day 4 post transplant cyclophosphamide doses, not for the pre-transplant doses. At the doses used for uroprotection mesna is virtually non-toxic. However, adverse effects which may be attributable to mesna include nausea and vomiting, diarrhea, abdominal pain, altered taste, rash, urticaria, headache, joint or limb pain, hypotension and fatigue.

Fludarabine (Fludara®)

Fludarabine phosphate is purine antimetabolite that, after administration, undergoes rapid conversion in plasma to the nucleoside 2-fluoro ara-A (F-araA). F-araA subsequently enters cells where it is phosphorylated to F-araATP and the monophosphate F-araAMP. Once activated, F-araATP inhibits DNA polymerase and ribonucleotide reductase. The monophosphate F-araAMP, once incorporated into DNA, is an effective DNA chain terminator. Fludarabine monophosphate, 50 mg/vial, is reconstituted with 2 ml of sterile water, resulting in a 25mg/ml solution. The desired dose is further diluted to concentrations of 0.04-1 mg/ml in normal saline or 5% dextrose (50-100ml) for injection and will be administered by IV infusion over 30 minutes. Following IV administration, the drug is metabolized to 2-F-araA and widely distributed in tissues. 2-F-araA is excreted primarily in urine and has a terminal elimination half-life of 7 to 12 hours. Clinical toxicities of fludarabine monophosphate include: myelosuppression, primarily lymphopenia and granulocytopenia, alopecia, rash, dermatitis, nausea, vomiting, anorexia, stomatitis, diarrhea, somnolence, fatigue, peripheral neuropathy, mental status changes, cortical blindness, hepatocellular toxicity with elevation in serum transaminases, and interstitial pneumonitis. These effects are reversible when the drug is discontinued.

Tacrolimus

Tacrolimus, also known as FK-506, is a macrolide immunosuppressant. It inhibits lymphocytes by forming a complex with FKBP-12, calcium, and calmodulin, leading to the decrease in the phosphatase activity of calcineurin. This drug is used with corticosteroids for prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. Its use is also

currently being investigated in bone marrow, pancreas, pancreatic islet cell and small bowel transplantation. This drug is well-absorbed orally. Tacrolimus is extensively metabolized by the mixed-function oxidase system, primary the cytochrome P450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation in vitro. . The metabolized products are excreted in the feces and urine. Nephrotoxic drugs, antifungals, calcium channel blockers, cimetidine, danazol, erythromycin, methylprednisone and metoclopramide increase the bioavailabilty of FK-506. In contrast, phenobarbital, phenytoin, rifamycins and carbamazepine decrease FK-506 levels. Adverse reactions include tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction.

Total Body Irradiation

Patients as part of their BMT preparative regimen will receive 200 cGy of TBI in one fraction on day -1. The prescription point is located at the midplane of the body at the level of the umbilicus. The dose uniformity as measured by the dose to the reference point (umbilicus) is kept within + 10% of the prescribed dose. An interruption in the radiotherapy regimen should only be considered if the patient has developed potentially life threatening complications that preclude continuation of the radiotherapy schedule. The dose rate will be less than 10cGy/min at the prescription point and should be recorded for each treatment as well as the total time of the treatment in order to compute the effective dose rate per treatment field.

Graft Failure

A risk of participating in this research protocol is that shifting part of the standard HSCT dose of cyclophosphamide after the graft infusion may damage the graft. The consequences of damaging the graft may include delayed hematologic recovery or graft failure. The risk of delayed hematologic recovery does not appear to be severe, based on prior experience with nonmyeloablative haploidentical transplantation. However, the risks of delayed hematologic recovery in this study cannot be directly extrapolated from referenced studies due to the inclusion of the investigational drug, MLN9708, in this protocol. Primary graft failure in the setting of a nonmyeloablative preparative regimen is usually not a fatal complication, as autologous hematopoietic recovery is usually expected.

Acute and Chronic GVHD

The second major risk in participating in this research protocol is the risk of developing acute and/or chronic GVHD. The degree of GVHD varies from mild cutaneous reactions to extensive widespread and systemic involvement of skin, liver, and gastrointestinal tract. The incidence of fatal infection is greater in patients developing GVHD due to the immunosuppressive nature of GVHD and its associated treatments. The development of grade 3 or higher acute GVHD is considered clinically significant and associated with increased morbidity and non-relapse mortality. The likelihood of surviving severe GVHD is to a large part dependent on the age of the patient and the patient's overall condition. For the majority of the patients eligible for this trial who have high-risk hematologic malignancies, a moderate increase in GVHD may be accompanied by an increased graft-versus-malignancy (GVM) benefit, so that the same long-term relapse free survival is maintained.

Regimen-related toxicities

Toxicities directly related to the administration of high-dose chemotherapy and TBI include gastrointestinal toxicity (nausea, vomiting, mucositis), alopecia, infertility (which may be permanent), interstitial pneumonitis, idiopathic cardiomyopathy, hemorrhagic cystitis, hepatic venoocclusive disease, or multi-organ failure which may be fatal.

Infection

Infection is a major cause of morbidity in allo HSCT and is a major concern in these patients. Infections may be bacterial, viral, parasitic, or fungal. Often, these infections are life-threatening, particularly when caused by viral or fungal organisms, and are associated with high mortality in the transplant population.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To estimate the incidence of relapse/progression at one-year post-transplant.

2.2 Secondary Objectives

- To obtain estimates of overall survival (OS), event-free survival (EFS), non-relapse mortality (NRM), engraftment, acute and chronic graft-versus-host disease (GVHD).
- Characterize additional hematologic and non-hematologic toxicities of MLN9708 when given post haploidentical transplant.
- Characterize donor hematopoietic chimerism in peripheral blood at days ~30, ~60, and ~90 after HSCT.

3. STUDY ENDPOINTS

3.1 Primary Endpoints

- Relapse/Progression

3.2 Secondary Endpoints

- OS, EFS, NRM, engraftment, acute and chronic GVHD
- Unexpected toxicities attributable to MLN9708
- Donor hematopoietic chimerism

4. STUDY DESIGN

4.1 Overview of Study Design

Patients will be required to meet institutional guidelines for transplantation and follow the institutional standard for post-transplant care. At a minimum, patients will need to be seen for study related purposes according to the following schedule. Other tests and exams will be done according to physician preference.

Test	Screen	Month 1 (4 weekly visits)	Month 2 (4 weekly visit)	Month 3 (4 weekly visits)	Month 4	Month 5	Month 6	Months 7-11	Month 12	End of Study	Months 18, 24 and 36
H & P	X	X	X	X	X	X	X	X	X	X	X
CBC with differential	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X
PFT*	X										
ECHO*	X										
IDMs including Hepatitis & HIV*	X										
Pregnancy test **(FOCBP)	X										
GVHD assessment		X	X	X	X	X	X	X	X	X	X
Toxicity Assessment		X	X	X	X	X	X	X	X	X	X
Bone marrow biopsy & aspirate				X			X		X	X	X
CT/PET for NHL/HD for disease assessment				X			X		X	X	X
Research Sample***	X	X (Day 30)	X (Day 60)	X (Day 90)			X		X		
Survival											X
New malignancy assessment											X

*Testing that is done for transplant is acceptable if done within 6 weeks of the start of study drug.

**Women with a uterus <50 or women >50 but < one year without a menstrual cycle) are considered FOCBP.

*** Research samples will be collected for lymphocyte subsets. Additional PBMCs will be collected to be frozen for future immune reconstitution studies. Approximately 30-50ml of blood will be collected at each time point.

MLN9708 will be given weekly x 3 weeks every 28 day cycles, for up to 12 cycles starting at D+5 post-transplant.

4.2 Number of Patients

Twenty-five (25) patients will be enrolled on this study. Should a patient sign consent and either not be transplanted or elect not to start MLN9708, they will be considered a screen failure. Patients who have begun high dose chemotherapy and decide not to start MLN9708 will be placed on mycophenolate mofetil 15 mg/kg actual body weight orally three times daily (maximum total daily dose of 3 grams) through day +35 in addition to tacrolimus for GVHD prevention.

4.3 Duration of Study

Patients have the potential to continue on active study treatment for up to 12 months post-transplant depending on disease assessment. Adverse events will be collected for 30 days post the last dose of study drug given. Patients will be followed for survival per institutional guidelines at a minimum of 18, 24 and 36 months post-transplant.

4.4 Correlative Samples

Patients will be asked to participate in optional research. Correlative samples will be drawn at baseline, day 30, 60, 90, 6mo, 12 months for flow cytometric analysis for T cell and NK cell recovery. Additional PBMCs will be collected and frozen for future immune reconstitution studies, including T cell receptor spectratyping and flow cytometric measurement of naïve, memory, and regulatory T cell reconstitution. Approximately 30-50ml of blood will be collected at each time point.

5. STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Availability of a 3/6 – 5/6 matched (HLA-A, B, DR) related donor

    - Donor must have negative HLA cross-match in the host vs. graft direction.
    - Donor must be willing to donate mobilized peripheral blood stem cells

2. Male or female patients Age ≥ 18 years

3. Karnofsky status ≥ 70% *(Appendix 1)

4. 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.

5. One of the following high-risk malignancies:

    Chronic Myelogenous Leukemia

    - Chronic myelogenous leukemia in chronic phase, resistant and/or intolerant to tyrosine kinase inhibitors (OR)
    - Chronic myelogenous leukemia in accelerated phase (OR)
    - Chronic myelogenous leukemia with blast crisis that has entered into a second chronic phase following induction chemotherapy.

    Acute Myelogenous Leukemia

    - 2nd or subsequent complete remission (OR)
    - Primary induction chemotherapy failure, but subsequently entered into a complete remission (OR)
    - 1st complete remission with poor risk cytogenetics or molecular markers; or arising from preceding hematological disease

    Myelodysplastic Syndrome

    - Treatment-related
    - Monosomy 7 or complex cytogenetics

- IPSS score of 1.0 or greater
- Chronic myelomonocytic leukemia (CMML)

Acute lymphocytic leukemia/lymphoblastic lymphoma

- 2nd or subsequent complete remission (OR)
- Primary induction chemotherapy failure, but subsequently entered into a complete remission (OR)
- 1st complete remission with poor risk cytogenetics

Chronic Lymphocytic Leukemia / Prolymphocytic Leukemia

- Duration of remission <12 months after receiving chemotherapy with a nucleoside analog (OR)
- High risk features (i.e. 17p deletion), (OR)
- Second or subsequent relapse

Hodgkin's or Non-Hodgkin's Lymphoma (including low-grade, mantle cell, and intermediate-grade/diffuse)

- Previously treated disease that has either relapsed or failed to respond adequately to conventional-dose therapy or autologous transplantation (AND)
- Chemoresponsive to most recent salvage therapy

Multiple Myeloma

- Presence of a poor risk cytogenetic abnormality [i.e. 17p, t(4;14)]
- Relapse post autologous transplant

5.2 Exclusion Criteria

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

1. Patients will not be excluded on the basis of sex, racial or ethnic background.

2. Prior allogeneic transplant

3. Poor cardiac function: left ventricular ejection fraction <40%

4. Poor pulmonary function: FEV_1, FVC, or DLCO <50% predicted

5. Poor liver function: bilirubin ≥2.5 mg/dl (not due to hemolysis, Gilbert's or primary malignancy), AST/ALT > 3X ULN

6. Poor renal function: Creatinine ≥2.0 mg/dl or creatinine clearance (calculated creatinine clearance is permitted) < 40 mL/min

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

8. Women of childbearing potential who currently are pregnant or who are not practicing adequate contraception

9. Patients who have any debilitating medical or psychiatric illness which would preclude their giving informed consent or their receiving optimal treatment and follow-up.

10. Systemic treatment, within 14 days before the first dose of MLN9708, with strong 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.

11. Patient has ≥ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.

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

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

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

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

16. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 including difficulty swallowing.

5.3 Criteria for donor selection

1. Donors will be family members haploidentically matched to the recipient at least 5/10 loci (HLA-A, B, C, DR, DQ). Half siblings are permitted as donors.

2. Donors must be willing to donate mobilized peripheral blood progenitor cells.

3. Donors will be selected to avoid both a positive HLA crossmatch in the host-versus-graft (HVG) direction and/or high titer donor specific antibodies as determined by the pre-transplant panel reactive antibody (PRA) testing.

4. Donors will be selected preferentially to maximize NK alloreactivity in the following order of preference. Priority will be given to donors with inhibitory Kir-ligand mismatches in the GVH direction. In the setting of multiple possible NK alloreactive donors, preference will be given to donors having a group "B" Kir haplotype. If no NK alloreactive donors are available, preference will be given to donors with the highest group B haplotype content[28] (appendix 2).

6. TREATMENT PLAN / STUDY DRUG

6.1 Transplant Regimen

Peripheral Blood Stem Cell Collection

Peripheral blood stem cells will be collected by institutional guidelines following standard G-CSF-based mobilization and infused on day 0. Cryopreservation of the stem cell product prior to infusion is permissible.

Stem Cell Processing

Minor ABO incompatible stem cell grafts will be plasma reduced and washed. Major ABO incompatible stem cell products will not require manipulation.

Preparative Regimen

- **Fludarabine** 30 mg/m^2 infused over 30 minutes once daily on days -6, -5, -4, -3 and -2 (total dose, 150 mg/m^2).
- **Cyclophosphamide** 14.5mg/kg/d infused over 1-2 hours once daily on days -6 and -5
- **TBI** 200 cGy to be administered in 1 fraction on day -1.

Stem Cell Infusion (Day of Transplant) day 0.

Post-transplant Cyclophosphamide

- **Cyclophosphamide** 50mg/kg will be given on D+3 post-transplant (within 72 hr of PBSC infusion) and on D+4 post-transplant. Cyclophosphamide will be given as an IV infusion over 2 hours. Hydration and Mesna will be given according to the institution's standard of care.

Chemotherapy Dosing:

Fludarabine dose will be based on actual body weight. Cyclophosphamide pre-transplantation dose is based on the lesser of adjusted ideal body weight or actual body weight. Cyclophosphamide post-transplantation dosing weight is based on the lesser of actual or ideal body weight.

- Ideal Body Weight (IBW) Formulas:

  Males IBW = 50 kg + 2.3 kg/inch over 5 feet

  Females IBW = 45.5 + 2.3 kg/inch over 5 feet

  For patients less than 5 feet, subtract 2.3 kg/inch

- Adjusted Ideal Body Weight (AIBW) Formula:

  AIBW = IBW + [(0.25) x (ABW – IBW)]

- Doses of Fludarabine will be adjusted as needed according to creatinine clearance:

  Creatinine Clearance = (140-Age) x IBW (x 0.85 for females)

72 x Serum Creatinine

CHEMOTHERAPEUTIC AGENT	**Calculated Creatinine Clearance** **46-60 ml/min**	**Calculated Creatinine Clearance** **31-45 ml/min**
Fludarabine	80% of total dose	75% of total dose

Growth factor support: Patients will receive G-CSF (Filgrastim) 5 mcg/kg/d SQ starting day +5 and continuing until the ANC >1000/mm^3 x 3 days or 1500/mm^3 x 1 day.

Supportive Care: Antibiotic prophylaxis and other supportive care measures will be implemented according to institutional guidelines. Ciprofloxacin is not permitted while receiving MLN9708 due to its inhibition of CYP1A2; however alternative floroquinolones are acceptable (levofloxacin, moxifloxacin, gatifloxacin). Broad-spectrum azole anti-fungal medications such as voriconazole, posaconazole, or itraconazole are not permitted while receiving MLN9708 due to its inhibition of CYP3A4. Acceptable anti-fungal prophylaxis medications include the echinocandins (i.e. Micafungin) or liposomal Amphotericin (i.e. Ambisome).

Post-transplant immunosuppression:

- **It is crucial that NO immunosuppressive agents are given until 24 hours after the completion of the post-transplant Cyclophosphamide. This includes steroids as anti-emetics**.

- Tacrolimus 0.03mg/kg/day infuse over 24 hours starting on day+5 (adjusted to maintain a trough level of 5-15 ng/ml) and switched to oral (twice-daily divided dose) on day 21 or when able to tolerate p.o. Tacrolimus will be discontinued on day +180, in the absence of clinically significant GVHD.

MLN9708 **(Ixazomib®)**:

- MLN9708 will be administered orally weekly x 3doses q28days, up to 12 monthly cycles, starting at day +5 post-transplant (see section 6.2).
- It will be given at a fixed dose of 4mg po with dose adjustment for hematologic or non-hematopoietic toxicity (see section 6.3).

6.2 MLN9708 Administration

MLN9708 Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients should be monitored for toxicity, as necessary, and doses of MLN9708 should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of MLN9708 dose (see Section 6.3).

Capsules of MLN9708 will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 2.3, 3.0 and 4.0 mg MLN9708. MLN9708 will be administered at a fixed dose of 4mg orally weekly x 3doses, q28days, up to 12 monthly cycles, starting at day +5 post-transplant, with dose adjustment for hematologic or non-hematopoietic toxicity (see Section 6.3).

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

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed doseIn case of vomiting repeat doses should be given as follows:

1. If vomiting occurs within 30 minutes of taking a dose and the capsule is found then the entire dose should be repeated. Repeat dosing should occur as soon as nausea has resolved. Unexpected delays in repeat dosing are acceptable as long as dosing is complete at least 72 hours before the next scheduled dose.

2. If vomiting occurs within 30 minutes of taking a dose and no capsule is found then 50% of the dose should be repeated. Patients assigned dose level -2 (2.3mg) will receive 1.5mg as the repeat dose. Repeat dosing should occur as soon as nausea has resolved. Unexpected delays in repeat dosing are acceptable as long as dosing is complete at least 72 hours before the next scheduled dose.
3. If vomiting occurs 30-60 minutes after a dose then 50% of the dose should be repeated, regardless of vomitus contents. Patients assigned dose level -2 (2.3mg) will receive 1.5mg as the repeat dose. Repeat dosing should occur as soon as nausea has resolved. Unexpected delays in repeat dosing are acceptable as long as dosing is complete at least 72 hours before the next scheduled dose.
4. If vomiting occurs more than 60 minutes after a dose the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

MLN9708 Destruction

Investigational MLN9708 (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Removal and destruction of all drug will be documented on drug accountability logs.

6.3 Dose-Modification Guidelines

6.3.1 Recommended MLN9708 Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

Treatment with MLN9708 will use a cycle length of 28 days. Cycle #1 will begin regardless of ANC or platelet count and continue for the full cycle. During cycle #1, MLN9708 will only be held or dose modified for grade 3-4 non-hematologic toxicity, judged to be related to study drug. If MLN9708 is held during cycle #1, mycophenolate 15mg/kg three times daily (3 grams maximum daily dose) may be given at MD discretion. For any new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be $\geq 1{,}000/mm^3$ (can be supported with growth factor support).
- Platelet count must be $\geq 50{,}000/mm^3$.
- All other nonhematologic toxicity (except for alopecia) must have resolved to $\leq$ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed until resolution of toxicity per tables 6-2 and 6-3.. The maximum delay

before treatment should be discontinued will be 4 weeks or at the discretion of the Principal Investigator.

For dosing recommendations upon recovery, refer to Table 6-2 and Table 6-3.

Table 6-1 MLN908 Dose Adjustments

Dose Level	Dose (mg)
Starting Dose	4.0 mg
-1	3.0 mg
-2	2.3 mg
-3	Discontinue

Dosage adjustments for hematologic toxicity are outlined in Table 6-2.

Table 6-2 MLN9708 Dose Adjustments for Hematologic Toxicities

Criteria	Action
• If ANC <1.0 x 10^9/L or platelet count <50x10^9/L prior to the start of a new cycle (other than cycle 1) OR • If platelet count falls to ≤30 x 10^9/L or ANC≤0.50 x 10^9/L after initiating a cycle but before day 15	• Hold MLN9708 until resolution as per section 6.2 • Upon recovery, MLN9708 may be reinitiated with 1 dose level reduction
• If platelet count falls to ≤30 x 10^9/L or	• Reduce MLN9708 by 1 dose level at the

ANC≤0.50 x 10^9/L after day 15 but recovers in time for the start of the next cycle	start of the next cycle

Treatment modifications due to MLN9708-related AEs are outlined in Table 6-3.

Table 6-3 MLN9708 Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only[60]
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2 (other than cycle 1)	• Hold study drug until resolution to Grade ≤ 1 or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)[60]
New or worsening Grade 2 peripheral neuropathy with pain (other than cycle 1) or Grade 3 (any cycle)	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated[60]
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 2 Rash	• Symptomatic recommendations as per section 6.6	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
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 6.7

Table 6-3 MLN9708 Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
If not recovered to < Grade 1 or baseline within 4 weeks	• Reduce study drug 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	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

Dose Re-Escalation:

- If MLN9708 is reduced for any nonhematologic toxicity judged related to study drug, the dose may not be re-escalated.
- If MLN9708 is reduced for hematologic toxicity, the dose may be re-escalated at the discretion of the principal investigator.

6.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. A DDI with a strong inhibitor would increase MLN2238 exposure.

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

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use. A DDI with a strong inducer would decrease MLN2238 exposure.

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

The use of NSAIDS should be avoided

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

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against hematologic malignancies except for drugs in this treatment regimen
- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).

6.5 Permitted Concomitant Medications and Procedures

- G-CSF (filgrastim) will be given post transplant as described in section 6.1. Erythropoietin, if used, should follow published guidelines and/or institutional practice.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.6 Precautions and Restrictions

Fluid deficits should be corrected before and throughout treatment.

Nonsteroidal anti-inflammatory drugs (NSAIDs) induced prevalence of nephrotoxicity is relatively low; however, given the wide use of these agents many persons are at risk, including for example, patients with cardio-renal disease, dehydration, and the aging kidney. NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Pregnancy

It is not known what effects MLN9708 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following criteria:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, AND
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

6.7 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with MLN9708 treatment. Management guidelines regarding these events are outlined below. Further details of management of MLN9708 AEs are described in Section 6 of the MLN9708 IB.

Use of MLN9708 in the setting of graft-versus-host disease (GVHD)

In the setting of grade II-IV acute GVHD or moderate-severe cGVHD, MLN9708 should be discontinued. Upon resolution of GVHD, consideration could be given to restarting investigational drug at the discretion of the principal investigator.

Prophylaxis Against Risk of Infection

If lymphopenia is noted, patients may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses.

Antiviral therapy such as acyclovir or valacyclovir may be initiated as clinically indicated. Other antivirals are also acceptable.

Nausea and/or Vomiting

Standard anti-emetics, including 5-HT_3 antagonists, are recommended for emesis occurring upon treatment initiation; prophylactic anti-emetics may also be considered. . Fluid deficits should be corrected before initiation of study drug and during treatment.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of anti-diarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficits should be corrected before initiation of treatment and during treatment. Prophylactic anti-diarrheals are not generally recommended.

Erythematous Rash With or Without Pruritus

As with VELCADE, rash with or without pruritus has been reported with MLN9708, primarily at the higher doses tested. The rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body or more generalized, has been transient and has resolved either spontaneously or with standard symptomatic measures such as oral or topical steroids and/or antihistamines. Prophylactic measures should also be considered if a patient develops a rash (e.g., using a thick, alcohol-free emollient cream on dry areas of the body). A rare risk is Stevens-Johnson Syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice.

Thrombocytopenia

Thrombocytopenia has been reported to date primarily at the higher doses tested. 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. Thrombocytopenia nadirs commonly recover without intervention by the beginning of the next scheduled cycle. MLN9708 administration should be modified as noted as per dose modification recommendations in Table 6-2 when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), 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. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Neutropenia has been reported with MLN9708. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable with G-CSF according to standard clinical practice. Neutropenic nadirs commonly recover without intervention by the beginning of the next scheduled cycle or with a short delay in treatment. MLN9708 administration should be modified when neutropenia occurs, as noted in the dose modification recommendations in Table 6-2. Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

Fluid Deficits

Dehydration should be avoided because MLN9708 may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported with MLN9708. Fluid deficits should be corrected before initiation of study drug and during treatment and as needed during therapy. Until further information is available, intake of NSAIDs while on this protocol should be avoided.

Hypotension

Symptomatic hypotension and orthostatic hypotension 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 anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES) has been reported with MLN9708. While this case ultimately resolved, PRES has also been reported rarely with another proteasome inhibitor, VELCADE. PRES is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Prompt diagnosis and initiation of antihypertensive and anticonvulsant therapy are important to prevent irreversible end-organ damage.

6.8 Preparation, Reconstitution, and Dispensing

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

6.9 Packaging and Labeling

The study drug MLN9708 capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

MLN9708 capsules should be stored unopened at 2°C to 8°C (36°F-46°F). The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. The 0.2-, 0.5-, and 2.0 mg capsules are in 1 × 4 blister strips that are individually perforated. The strips (1 × 4) are placed in cartons containing 6 strips (24 total capsules) of the same strength. The 2.3-, 3.0-, and 4.0 mg capsules are supplied as a 1 x 3 blister card in a child-resistant cardboard wallet.

6.10 Storage, Handling, and Accountability

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

In countries where local regulations permit, MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

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

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

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

6.11 Study Compliance

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

6.12 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Lost to follow-up
- Progressive disease
- Study terminated
- Other

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

7. STATISTICAL AND QUANTITATIVE ANALYSES

Statistical Methods

7.1.1 Determination of Sample Size

The primary endpoint of this trial will be the risk of relapse and/or progression at one-year post-transplant. Experience from the literature suggests that following a nonmyeloablative haploidentical transplant using post-transplant cyclophosphamide (haplo-pCy), the risk of relapse is approximately 50% at one year post-transplant[61]. It is hoped that under this protocol, this rate will be at most 25%. Thus we statistically formalize this study by testing the null hypothesis that p, the PFS rate is 0.25 or less versus the alternative hypothesis that p is greater than 0.5. A sample size of 25 patients gives 90% power with an alpha=0.05, using the formula for a one sample binomial (two-sided) test of a proportion. Accrual will continue unless a stopping criterion is met. We expect that patients will be accrued over 2 years.

7.1.2 Stopping Criteria

NRM: As outlined in Section 1 (Background), the overall non-relapse mortality (NRM) on the nonmyeloablative haploidentical HSCT trial utilizing post-transplantation Cy, MMF and tacrolimus is approximately 19% at one year. Consequently a NRM incidence that is convincingly greater than 20% would raise concerns for excessive toxicity. This trigger would be met if NRM occurs in 3 out of the first 5 patients, 5 of the first 10 patients, or 6 of the first 15 patients. If the stopping criterion is met, accrual to the trial will be temporarily halted until a decision regarding either modification or termination of the trial could be made.

Severe acute GVHD (aGVHD): As outlined in Section 1 (Background), the expected incidence of severe aGVHD (Grades III-IV)) on the nonmyeloablative haploidentical HSCT utilizing post-transplantation Cy, MMF and tacrolimus is approximately 10%. The working hypothesis of this trial is that the overall toxicity of fully ablative haploidentical HSCT is not significantly greater than haploidentical HSCT after nonmyeloablative conditioning utilizing post-transplantation Cy. Consequently, an incidence of severe aGVHD convincingly greater than 15% would raise concerns for excessive toxicity. This trigger would be met if severe aGVHD occurs in 3 of the first 5 patients, 4 of the first 10 patients, or 5 of the first 15 patients. If the stopping criterion is

met, accrual to the trial will be temporarily halted, until a decision regarding either modification or termination of the trial could be made.

Engraftment Failure: As outlined in Section 1 (Background), the incidence of engraftment failure on the nonmyeloablative haploidentical HSCT trial utilizing post-transplantation Cy, MMF and tacrolimus is approximately 18%. Consequently a graft failure incidence that is convincingly greater than 20% would raise concerns for excessive toxicity. This trigger would be met if graft failure occurs in 3 out of the first 5 patients, 5 of the first 10 patients, or 6 of the first 15 patients. If the stopping criterion is met, accrual to the trial will be temporarily halted until a decision regarding either modification or termination of the trial could be made.

Excessive Toxicity (defined as toxicities CTCAE v.3 grade 4 or higher considered probably or definitely related to the study drug): There is significant potential and/or expected toxicity that occurs in the first 4 weeks following allogeneic transplant, including severe cytopenias (neutropenia, anemia, thrombocytopenia), renal insufficiency, hypokalemia, hypomagnesaemia, hepatic sinusoidal obstruction syndrome, nausea, vomiting, diarrhea, mucositis/enteritis, fever, life-threatening infections, thrombotic microangiopathy, graft rejection, and graft-versus-host disease. However, excessive toxicity that is convincingly greater than 15% would raise concerns. This trigger would be met if grade ≥4 toxicity, probably or definitely related to study drug, occurs in the first four weeks in 3 out of the first 5 patients, 4 of the first 10 patients, or 5 of the first 15 patients. If the stopping criterion is met, accrual to the trial will be temporarily halted until a decision regarding either modification or termination of the trial could be made.

8. ADVERSE EVENTS

Definitions

8.1.1 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.

8.1.2 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.

8.1.3 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 (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

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.

8.1.4 Adverse Event of Special Interest Definition

Adverse Events of Special Interest (AESIs) are a subset of AEs that are to be reported to Millennium on a quarterly basis by the sponsor-investigator. Millennium will provide the current list of AESIs and updates to the list will be distributed to the sponsor-investigator as appropriate

8.2 Procedures for Reporting Serious Adverse Events

AEs may be 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. 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 one comprehensive event. For serious 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.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the date the participant receives the first dose of study drug through 30 days after administration of the last dost of MLN9708. Any SAE that occurs at any time during treatment with MLN9708 or for 60 days after the completion of MLN9708 treatment that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

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 (e.g., surgery was performed earlier or later than planned). 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).

Since this is an investigator-initiated study, the principal investigator, Scott R. Solomon, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor-investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to Millennium Pharmacovigilance:

Fatal and Life Threatening SAEs within 24 hours but no later than 4 calendar days of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The protocol may include language to specify expected adverse events which will not be considered serious and will not require expedited reporting.

The sponsor-investigator must fax the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

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

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

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

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study or study drug(s), including, but not limited to, telephone conversation logs within 24 hours but no later than 4 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information

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

Suggested Reporting Form:

- SAE Report Form (a sample is provided in Appendix 13.3)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

8.3 Procedures for Reporting AESIs

AEs may be 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. 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 one comprehensive event. For nonserious AEs

(including AESIs), the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

AESIs must be reported to Millennium on a quarterly basis.

8.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (a sample is provided in Appendix 12.)

9. ADMINISTRATIVE REQUIREMENTS

9.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (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 Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

9.2 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 in order 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, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB/IEC submission.

9.3 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.

9.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. If requested, the investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.5 Investigator Compliance

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

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

9.6 On-site Audits

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

9.7 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium or a designee or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

9.8 Product Complaints

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 MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
call MedComm Solutions at
877-674-3784 (877 MPI DRUG)
(US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 8.2).

9.9 Closure of the Study

This 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 drug

9.10 Record Retention

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

10. 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.

11. DISEASE EVALUATION[62, 63]

Relapse of Malignancy – Testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. For the purpose of this study, relapse is defined by either morphological or cytogenetic evidence of acute leukemia consistent with pre-transplant features, or radiologic evidence (including the recurrence of fluoro-deoxyglucose [FDG]-avid lesions on PET scan) of progressive lymphoma. When in doubt, the diagnosis of recurrent or progressive lymphoma should be documented by tissue biopsy.

Minimal Residual Disease – Minimal residual disease is defined by the sole evidence of malignant cells by flow cytometry, or fluorescent in situ hybridization (FISH), or Southern blot, or Western blot, or polymerase chain reaction (PCR), or other techniques, in absence of morphological or cytogenetic evidence of disease in blood or marrow. Since the frequency of testing for minimal residual disease is highly variable among centers, and the sensitivity is highly variable among laboratory techniques, evidence of minimal residual disease alone will not be sufficient to meet the definition of relapse in the context of this trial. However, minimal residual disease that progresses (see above) will be considered as relapse and the date of relapse will be the date of detection of minimal residual disease that prompted an intervention by the treating physician. Data on tapering immunosuppression, administering chemotherapy or biological agents to in response to detection of minimal residual disease will be captured in the case report forms.

Acute Leukemia – Relapse will be diagnosed when there is:

1. The reappearance of leukemia blast cells in the peripheral blood; or,
2. > 5% blasts in the marrow, not attributable to another cause (e.g., bone marrow regeneration); or
3. The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid or
4. The reappearance of cytogenetic abnormalities present prior to transplantation

Lymphoma – Relapse will be diagnosed when there is:

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the sum of the product diameters (SPD) of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

   Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<.1.5 cm in its long axis by CT).

   Institution of any therapy to treat persistent, progressive or relapsed disease, including withdrawal of immunosuppressive therapy or DLI, will be considered evidence of relapse/progression regardless of whether the criteria described above are met.

TABLE 11.1 RESPONSE CRITERIA FOR LYMPHOMA[64]

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Response Criteria for Acute Leukemia

Remission is defined as < 5% blasts with no morphological characteristics of acute leukemia (e.g., Auer Rods) in a bone marrow with > 20% cellularity, peripheral blood counts showing ANC >1000/µl, including patients in CRp.

Response Criteria for Lymphoma

Response criteria for lymphoma are described in Table 11.1

Response Criteria for Multiple Myeloma

Stringent Complete Response (sCR):

- SCR requires, in addition to CR (defined below), all of the following
- Normal free light chain ration (FLC)
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

Complete Response (CR) requires *all* of the following:

- Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation. The presence of new monoclonal bands is consistent with oligoclonal immune reconstitution does not exclude CR:
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed;
- No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture dose not exclude CR)*; and,
- Disappearance of soft tissue plasmacytomas.

*If not clinically indicated, radiographs are not required to document CR.

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as partial responses (see below), providing the remaining criteria satisfy the requirements for partial response. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Near Complete Response (nCR): represents disease detected only by immunofixation and it is defined as[65,66]

- Presence of the original monoclonal paraprotein in serum and urine by immunofixation
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed;
- No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture dose not exclude CR)
- **Very Good Partial Response (VGPR)** requires, in addition to PR (defined below), all of the following:Serum or urine paraprotein detectable by immunofixation but not on electrophoresis,

  OR

- Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein <100mg/24 hours

Partial Response (PR) requires one of the following:

- Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein and/or reduction in 24 hour urinary monoclonal paraprotein either by greater than or equal to 90% or to <200mg/24 hours in light chain deisease.

- If the only measurable non-bone marrow parameter is FLC, greater than or equal to 50% reduction in the difference between involved and uninvolved FLC levels or a 50% decrease in level or involved FLC with 50% decrease in ratio.
- If the bone marrow is the only measurable parameter, greater than or equal to 50% reduction in bone marrow plasma cells given that the baseline count was greater or equal to 30%.
- Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).

Stable Disease (SD)

- Patients who do not meet criteria for sCR, CR, VGPR, PR or progressive disease are considered to have stable disease (SD).

Progression (PD) from CR or sCR requires one or more of the following:

- A reappearance of serum monoclonal paraprotein, with a level of at least 0.5 g/dL.
- 24-hour urine protein electrophoresis with at least 200 mg paraprotein/24 hours.
- Abnormal FLC levels of >10 mg/dl, only in patients without measurable paraprotein in the serum and urine.
- At least 10% plasma cells in a bone marrow aspirate or on trephine biopsy.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

Progressive Disease (PD) for patients <u>not</u> in CR or sCR, progressive disease requires one or more of the following:

- >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL.
- >25% increase in 24-hour urine protein electrophoresis, which must also be an absolute increase of at least 200 mg/24 hours.

- Absolute increase in the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl), only in patients without measurable paraprotein in the serum and urine.
- >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of a compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

Response Criteria for CML[67]

Complete Hematologic response or remission (all must be present):

- Platelet count <450,000/ uL
- WBC count <10,000/UL
- No immature neutrophils
- <5% basophils
- Spleen not palpable

Cytogenetic Response

- No response >95% Ph+ cells
- Minor Response 36-95% Ph+ cells
- Major Response <35% Ph+ cells

Molecular response/remission

- Major response >3 log reduction

Complete response no BCR-ABL transcript detectable

Response Criteria for CLL[68]

Complete response

Requires all of the following for a period of at least three months from completion of therapy:

• Absence of lymphadenopathy > 1.5 cm on physical exam and CT scan;

• No hepatomegaly or splenomegaly on physical exam (CT scan may be used to assess);

• No clonal B-cells in the blood by flow cytometry;

• Normal CBC as exhibited by polymorphonuclear leukocytes ≥ 1500/μL, platelets > 100,000/μL, hemoglobin > 11.0 g/dL (untransfused); lymphocyte count < 5,000/μL;

• Bone marrow aspirate and biopsy must be normocellular for age with < 30% of nucleated cells being lymphocytes. Flow cytometry/immunohistochemistry should be performed on bone marrow. Lymphoid nodules may be present but must be T-cell in origin. If these are demonstrated to be clonal B-cells, patients should be considered a partial response. Additionally, if bone marrow is positive by two color flow cytometry for CLL cells it should be considered a partial response. If the marrow is hypocellular a bone marrow should be performed in 2-3 months. If blood counts (polymorphonuclear leukocytes < 1500/μL, platelets < 100,000/μL) fail to recover at the time of the response evaluation but there is otherwise no evidence of CLL otherwise, a repeat determination should be performed at the time of count recovery (polymorphonuclear leukocytes ≥ 1500/μL, platelets > 100,000/μL) but no later than six months.

• Patients who fulfill the criteria for CR after induction with the exception of a persistent cytopenia (CR with incomplete recovery, CRi) that is believed to be treatment related will be considered a CRi. As stated above, patients falling into this category should ideally undergo a repeat bone marrow when counts recover fully. If the bone marrow at this time reveals no CLL, these patients will be considered to be in complete remission at that time. Additionally, patients who fulfill the criteria of CR with exception of having bone marrow lymphoid CLL nodules will be considered a CRi and assessed prospectively for the similarity to outcome with CR.

Partial Response

Requires a ≥ 50% decrease in peripheral lymphocyte count from pre-treatment value, ≥ 50% reduction in lymphadenopathy of as many as 6 measurable lymph nodes, and/or ≥ 50% reduction in splenomegaly/hepatomegaly for a period of at least two months. Patients may have bone marrow lymphoid nodules of B-cell origin. Additionally, these patients must have one of the following:

• Polymorphonuclear leukocytes ≥ 1,500/μL or 50% improvement from pre-treatment value;

• Platelets > 100,000/μL or 50% improvement from pre-treatment value;

• Hemoglobin > 11.0 g/dL (untransfused) or 50% improvement from pre-treatment value

Progressive Disease

Characterized by any one of the following events:

• ≥ 50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥ 2 cm); appearance of new palpable lymph nodes.

• ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.

• ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5,000/μL.CALGB 100701/BMT CTN 0804 03/15/13 50

• Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes).

• Patients not fulfilling the above criteria for progressive disease but demonstrating a decrease in hemoglobin > 2 g/dL (or < 10 g/dL), decrease > 50% in platelet or granulocyte count will not be rated as progressive disease because these may occur as both a consequence of therapy and of underlying CLL. A bone marrow biopsy in such settings is strongly encouraged.

Stable Disease

Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

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13. APPENDICES

13.1 Appendix 1: Karnofsky Performance Status Scale

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	

13.2 Appendix 2: Group B KIR Haplotype Determination

Group A and B KIR haplotypes have distinctive centromeric (Cen) and telomeric (Tel) gene-content motifs. With the goal of developing a donor selection strategy to improve transplant outcome, Cooley et al., compared the contribution of these motifs to the clinical benefit conferred by B haplotype donors[28]. Compared to A haplotype motifs, centromeric and telomeric B motifs both contributed to relapse protection and improved survival, but Cen-B homozygosity had the strongest independent effect.

A donor KIR B-content group calculator is available through the Immuno Polymorphism Database (IPD) project, established by the HLA Informatics Group of the Anthony Nolan Research Institute in close collaboration with the European Bioinformatics Institute; and can be accessed through the following website: http://www.ebi.ac.uk/ipd/kir/donor_b_content.html.

13.3 Sample SAE Form

(A sample Serious Adverse Event Form is attached.)

13.4 Millennium Pregnancy Reporting Form

(A sample Pregnancy Form is attached)