CLINICAL STUDY PROTOCOL

(IISR-2012-M100016)

X16016

Phase I Study Of Vincristine, Doxorubicin, And Dexamethasone (VXD) Plus Ixazomib In Adults With Relapsed Or Refractory Acute Lymphoblastic Leukemia/Lymphoma, Lymphoblastic Lymphoma Or Mixed Phenotype Acute Leukemia

Indication:	Relapsed or refractory acute lymphoblastic leukemia/lymphoma, Lymphoblastic Lymphoma Or Mixed Phenotype Acute Leukemia
Phase:	Phase I

Protocol History

Original	8th, August, 2013
Amendment 1	4th, June 2014
Amendment 2	31st, July 2014
Amendment 3	2nd, June 2015

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PROTOCOL SUMMARY

Study Title: Phase I Study Of Vincristine, Doxorubicin, And Dexamethasone (Vxd) Plus Ixazomib In Adults With Relapsed Or Refractory Acute Lymphoblastic Leukemia/Lymphoma, Lymphoblastic Lymphoma Or Mixed Phenotype Acute Leukemia

Phase: I

Number of Patients: 9-18

Study Objectives

Primary Objectives

- The primary objective is to determine the maximum tolerated dose of VXD +ixazomib and to assess the tolerability of VXD + ixazomib in adult patients with relapsed or refractory acute lymphoblastic leukemia/lymphoma, lymphoblastic lymphoma or mixed phenotype acute Leukemia

Secondary Objectives

To estimate the overall response rate (ORR) including both complete remission (CR) and complete remission with incomplete count recovery (CRi) with VXD +ixazomib

Overview of rationale and Study Design:

In this phase I study, escalating doses of ixazomib will be combined with the VXD regimen.

The MTD of single agent ixazomib was 1.76 to 2.0mg/m^2 when given on a twice a week schedule and > 2.34 mg/m^2 to 2.97 mg/m^2 on a weekly schedule in previous studies[1-4]. The only reported combination study involved the combination of ixazomib with lenalidomide and dexamethasone[5]. In that study, escalating doses of IXAZOMIB from 1.68 to 3.95 mg/m^2 were given orally on days 1, 8, and 15 in combination with dexamethasone 40 mg on days 1, 8, 15, and 22 and lenalidomide 25 mg/day on days 1–21 every 28 Days. The MTD of ixazomib was 2.97 mg/m^2 and the recommended phase II dose (RP2D) was 2.23 mg/m^2. The dose limiting toxicities were skin rash, nausea and vomiting. The clinical development of ixazomib included a population PK analysis evaluating the feasibility of switching from BSA-based dosing to fixed dosing.[6] The results of this analysis support the transition to fixed dosing. In this trial our aim will be to escalate the dose to ixazomib orally to a dose of 4.0 mg (RP2D of 2.23 mg/m^2 $\times$ the mean patient BSA of 1.86 m^2).

Three patients will be treated per dose level unless dose limiting toxicity (DLT) is observed. The starting dose of ixazomib will be 2.3 mg orally on days 1, 8 and 15. If no DLT is seen in the first 3 patients, the dose will be increased to 3 mg and then to 4 mg orally on days 1, 8 and 15 in a classic 3 +3 phase I design. We will not attempt to increase the dose beyond 4 mg orally which, if achieved with acceptable toxicity, would be accepted as the recommended phase 2 dose (RP2D). 0 of 3 DLTs would allow escalation to the next dose level. 1 of 3 DLTs will require expanding to six patients; 1 of 6 DLTs will allow escalation again. 2 DLTs will require dose de-escalation. The maximum tolerated dose (MTD) will be the highest dose administered at which no more than 1 DLT was observed. All patients will be evaluated for hematopoetic stem cell transplantation (HSCT). If patients achieve CR and are eligible for HSCT, they will proceed to HSCT. If they

are not eligible, no donor is identified or if HSCT will be delayed, and the patient has achieved benefit, then treatment may be repeated for another cycle as clinically indicated.

Study Population:

Inclusion criteria

- Male or female patients 18 years or older
- Have relapsed B or T-precursor acute lymphocytic leukemia/lymphoma, lymphoblastic lymphoma or mixed phenotype acute leukemia with increased bone marrow or peripheral blood blasts by morphology with or without CNS involvement
- Prior therapy: At least two prior treatment attempts to induce remission with no limit on the number of prior treatment regimens.
- Patients may have received an allogeneic stem cell transplantation
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Patients must meet the following clinical laboratory criteria:
    - Direct bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN).
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN.
    - Calculated creatinine clearance ≥ 30 mL/min
    - Absolute neutrophil count (ANC) > 1,000/cmm and platelets > 75,000/cmm unless the cytopenias are secondary to disease
- Life expectancy adequate for evaluating the treatment effect per treatment physician discretion
- Patients must be at least 2 weeks from major surgery, radiation therapy, participation in other investigational trials and have recovered from clinically significant toxicities of these prior treatments
- Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR

- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form 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 [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

- Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one 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 (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

<u>Exclusion criteria</u>

- Patients who are Ph+ ALL who are naive to therapy with an approved tyrosine kinase inhibitor.
- Prior exposure to ≥350 mg/m2 of anthracycline (in doxorubicin equivalent dosing), or left ventricular fractional shortening less than 50%.
- Failure to have fully recovered (ie, ≤ Grade 2 toxicity) from the effects of prior chemotherapy regardless of the interval since last treatment.
- Major surgery within 14 days before enrollment.
- Chemotherapy in the last 14 days. (Steroids or Intrathecal chemotherapy will be allowed).

- Systemic treatment, within 7 days before study enrollment, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, or psychiatric illness/social situations that would limit compliance with study requirements. Patients receiving intravenous antibiotics for infections that are under control may be included in this study.

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

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

- Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

- Patient has ≥ Grade 2 peripheral neuropathy.

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

• Female patients who are breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.
Duration of Study: A minimum of 2 years

SCHEDULE OF EVENTS

Day	Screening[a]	Cycle 1 and 2 Week 1	Weekly	Q 2 weeks	Q 4 weeks	End of Study[b]	Follow-up
Informed consent	X						
Demographics	X						
Inclusion/exclusion criteria	X						
Medical History	X	X					
Medication history	X						
Concomitant medications	X	X		X		X	
Physical examination	X	X		X		X	
ECOG performance status	X	X		X			
Vitals	X	X		X		X	
Height and weight[c]	X	X[d]				X	
CBC with differential	X	X	X			X	
Serum Chemistry	X	X	X			X	

panel[e]							
Direct Bilirubin	X		X				
Fibrinogen	X	X	X				
Serum or urine pregnancy test	X	X [f]					
Cardiac Ejection Fraction (MUGA/Echocardiogram)	X	x[i]					
Bone marrow biopsy/aspirate [g]	X				X	X	
Adverse Event Reporting	Recorded from the first dose of study drug through 30 days after last dose of study drug						
Survival [h]							X

[a] Screening procedures to occur up to 14 days before Cycle 1 Week 1 Visit, except for pregnancy test (within 7 days prior to Week 1 Visit).
[b] Perform end-of-study procedures 4 weeks after study completion or at time of early withdrawal. If study procedure cannot be performed on the scheduled day, the procedure must be performed within 48 hours.
[c] Height will be measured at Screening only.
[d] Weight will be checked on day 1 of every cycle

[e] Including albumin, total protein, total bilirubin, ALT, AST, LDH, alkaline phosphatase, bicarbonate, sodium, potassium, chloride, creatinine, BUN, and glucose.
[f] Serum βHCG pregnancy test in female patients of childbearing potential does not need to be repeated for Cycle 1 Week 1 Visit if the screening test was completed within 72 hours of Cycle 1 Week 1.
[g] Bone marrow aspirate and/or biopsy and cytogenetics must be performed within 4 weeks prior to Week 1 Visit. Bone marrow biopsies at week 4 ±3 days
[h] Patients will be followed monthly until progression and then annually for survival.

[i] For cycle 2 only

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
apt	activated partial thromboplastin time
Ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BTZ	bortezomib
BUN	blood urea nitrogen
BZD	Benzodiazepines
CBC	complete blood count
CNS	central nervous system
CO_2	carbon dioxide
CR	complete remission

Abbreviation	Term
CT	computed tomography
CYP	cytochrome P_{450}
DDIs	Drug-Drug Interactions
DLT	dose-limiting toxicity
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)
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
HIV	human immunodeficiency virus

Abbreviation	Term
HSCT	Hematopoetic stem cell transplantation
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous; intravenously
LDH	lactate dehydrogenase
LFT	liver function test(s)
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
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
PD	progressive disease (disease progression)
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial remission

Abbreviation	Term
QD	*quaque die*; each day; once daily
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
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
TEAEs	treatment emergent adverse events (TEAEs)
ULN	upper limit of the normal range
US	United States
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Background

An estimated 6070 patients will be diagnosed with ALL in 2013, and 1 in 798 men and women will be diagnosed with ALL in their lifetime[7]. The median age for diagnosis of ALL is 14 years, and approximately 40% are >20 years old[8]. Despite the marked improvement in overall survival in children with ALL, treatment of ALL in adults remains challenging with 50-60% of patients dying of their disease.

Treatment of patients with newly diagnosed ALL:

Several regimens are currently utilized for the therapy of patients with newly diagnosed ALL with remarkably similar outcome. The two most commonly used regimens in the United States are the HyperCVAD regimen and the CALGB regimen. The HyperCVAD regimen is a multiagent intensive chemotherapy regimen composed of alternating cycles of cytoxan/doxorubicin/ vincristine/ dexamthasone alternating with high dose cytarabine and methotreaxte. All patients receive 4 to 16 intrathecal chemotherapy injections depending on risk stratification. Cranial irradiation was only given to patients with cranial nerve root involvement. In the phase II study of the HyperCVAD regimen, 288 patients were enrolled. Despite 92% percent of patients achieving CR, the 5 year survival was 38%. The other intensive multiagent chemotherapy regimen developed by the CALGB group utilizes several treatment blocks and included cytoxan, doxorubicin, vincristine, asparaginase and prednisone. All patients receive cranial irradiation and intrathecal chemotherapy for CNS prophylaxis. In the phase II study, 197 patients were enrolled. Again most patients achieved CR, but the 3 year estimated overall survival was 50%[i]

Treatment of relapsed ALL:

Several large retrospective studies have evaluated the outcome of adult patients with relapsed ALL. The PETHEMA (Programa Español de Tratamiento en Hematologia) group, analyzed the outcome of patients in first relapse. Of the 263 patients, 45% of patients achieved remission with a median overall survival of 4.5

months and 5 year survival of 10%. Age of patient and relapse > 2 years were the 2 major predictors of outcome[9]. In the MRC UKALL12/ECOG 2993 study, of the 1372 patients who entered remission, 609 (44%) relapsed. With a median follow up of 54 months, only 42 of the 609 patients were alive[10]. In another study by the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia, data of 547 patients with relapsed ALL were analyzed. The median survival was 8.4 months for all patients with a 3 year survival of 24%. The CR rate after first and second salvage was 42% and 33% respectively[11]. This CR rate in patients receiving second salvage therapy was very similar to the study by O'Brien et al. Of the 288 patients analyzed, only 18% achieved CR. The median duration of remission was 7 months with a median overall survival of 3 months[12]. In order to better define the outcome of pediatric patients with relapsed ALL, the Therapeutic Advances in Childhood Leukemia (TACL) consortium reported on patients with relapsed and refractory ALL previously treated at TACL institutions between the years of 1995 and 2004. The CR rate for patients in early first relapse, late first relapse, second and third relapse was 83%, 93%, 44% and 27% respectively. Five-year DFS rates in CR2 and CR3 were 27% ± 4% and 15% ± 7% respectively[13].

Several regimens are utilized in the treatment of patients with relapsed ALL. In a phase II study, 88 patients received the augmented HyperCVAD (augHyperCVAD) regimen. The augHyperCVAD is similar to the HyperCVAD regimen with the addition of asparaginase, and intensification of both dexamethasone and vincristine. The CR rate was 46% with a median survival of 6.3 months for the entire cohort. Eight (9%), of the patients died within the first 30 days. Seven of those deaths were secondary to infectious complications[14]. Another recently approved drug for the therapy of relapsed ALL in pediatric patients is clofarabine. In a phase II study, 61 pediatric patients with refractory or relapsed ALL received clofarabine 52 mg/m^2 intravenously over 2 hours daily for 5 days, every 2 to 6 weeks. The median age was 12 years (range, 1 to 20 years), and the median number of prior regimens was three (range, two to six regimens). Of those, 30% achieved CR/CRp. In another study by Miano et al, clofarabine (40 mg/m(2)/day), etoposide (100 mg/m(^{2})/day)

and cyclophosphamide (440 mg/m(^{2})/day) administered as one or two induction cycles over 5 days, was administered to patients with relapsed acute leukemia. Of the 40 children enrolled, 16 had AML and 24 had ALL. Of the 24 patients with ALL, 10 (42%) achieved CR. However, results of clofarabine combinations have been disappointing in adult patients with relapsed ALL. In a phase II study, 37 patients with relapsed refractory ALL were enrolled. Of those, only 17% patients achieved CR/CRp, and the median survival was 3 months[15]. Another recently approved drug for the therapy of relapsed T-cell ALL is nelarabine. Nelarabine is purine analogue with specific activity against T-cells. In a phase II study, 126 patients with relapsed or refractory T-cell acute lymphoblastic leukemia/lymphoma (ALL/LBL) were enrolled. Of those, 45 (36%) achieved CR. The overall survival was 24% at 1 year (11% at 6 years). The overall survival was 31% for patients who proceeded to HCT[16]. Nelarabine in combination with etoposide and cyclophosphamide has also been evaluated in a small number of patients and appeared to be safe[17].

The VXLD regimen (vincristine, doxorubicin, PEG asparaginase and dexamethasone) was evaluated in the pediatric group. In that study, 124 pediatric patients with ALL in first relapse were enrolled. Of those, 69 had early relapse (ER; < 36 months from initial diagnosis) and 55 with late relapse. The CR rate was 68% +/- 6% for patients with early relapse and 96% +/- 3% for patients with late relapse. No unexpected toxicities occurred. Hematological toxicity was the most common toxicity with neutropenia and thrombocytopenia occurring in 97.6 and 79.8% of patient respectively. Grade 3 or 4 toxicities which occurred with a higher than 10% incidence are detailed in Table (1). Overall 5 patients died on therapy and all were secondary to infections. Based on these results, the VXLD was chosen as the backbone for the therapy of patients with relapsed ALL to which various drugs would be added for evaluation[18]. Details of the VXLD regimen are shown in Table (2).

Table (1)

	VXLD (n = 124)	
Toxicity	**No.**	**%**
Febrile neutropenia	50	40.3
Fibrinogen	40	32.3
Hemoglobin	78	62.9
Hyperglycemia	15	12.1
Neutrophils/granulocytes (ANC/AGC)	121	97.6
Platelets	99	79.8
ALT	18	14.5
Transfusion		
Platelets	93	75.0
pRBCs	95	76.6

Based on the poor results previously discussed for adult patients with relapsed ALL, several new treatment approaches are currently being evaluated. These include monoclonal antibodies[19], bispecific antibodies[20] and proteosome inhibitors[21].

Several preclinical studies have shown that ALL cells are sensitive to proteosome inhibition and that there is a synergistic effect when the proteosome inhibitor (PI) bortezomib (BTZ) is combined with chemotherapy [22-24].

Proteosomes are expressed at abnormally high levels in human leukemic cell lines [25] leading to a study by Naujokat et al that evaluated the effect of proteosome inhibitors on human immature leukemic cell lines. Three proteosome inhibitors, lactacystin, benzyloxycarbonyl(Z)-leucyl-leucyl-leucinal (ZLLLal; MG-132) and 4-hydroxy-5-iodo-3-nitrophenylacetyl-leucyl-leucyl-leucine vinyl sulfone (NLVS),

induced apoptosis in leukemic cell lines CCRF-CEM, U937 and K562 as well as in myelogenic and lymphatic leukemia cells obtained from adults with relapsed acute leukemias. However, the proteosome inhibitors did not induce significant apoptosis in granulocytes and lymphocytes from the peripheral blood, suggesting a preferential effect on rapidly proliferating cells [26]. BTZ is a proteosome inhibitor with activity against multiple hematologic malignancies. It is currently FDA approved for the therapy of multiple myeloma and mantle cell lymphoma. BTZ was evaluated in a pediatric pre-clinical testing program and was found to have in vitro and in vivo activity [23]. For in vitro testing, BTZ was incubated with rhabdomyosarcoma, rhabdoid, Ewing sarcoma, glioblastoma, neuroblastoma, ALL, acute myelogenous leukemia (AML) and non Hodgkin lymphoma (NHL) cell lines. The median IC50 for ALL cell lines was significantly lower than the median IC50 for solid tumor lines (12 nM vs. 30 nM, $P < 0.0094$). For in vivo testing, BTZ was administered to mice intraperitoneally at 1 mg/kg twice weekly for 6 weeks and evaluated in 41 xenograft tumor models. There were no responses in the solid tumor xenograft models, while four of seven ALL xenografts demonstrated objective responses (two partial and two complete responses). Based on these findings, BTZ was evaluated as a single agent in a phase I study in patients with relapsed refractory acute leukemia. As a single agent, BTZ had minimal activity. Five of 15 patients had hematological improvement. Patients received a median of 5 doses with disease progression being the most common cause for discontinuation of drug[27].

In another preclinical study, BTZ potentiated the effect of chemotherapy [22]. BTZ was synergistic with dexamethasone and additive with vincristine, asparaginase, cytarabine, and doxorubicin. Based on the finding of synergism with corticosteroids, Messinger et al combined vincristine, pegasparaginase, dexamethasone and doxorubicin (VXLD) with escalating doses of BTZ in a phase I study. The standard dose of the VXLD regimen was used with no dose escalation of the chemotherapeutic agents. BTZ was escalated from 1 mg/m^2 to 1.3 mg/m^2 on D1, D4, D8 and D11. The investigators did not attempt to increase BTZ beyond 1.3 mg/m^2 which is the dose currently used in multiple myeloma. Ten patients with

relapsed refractory ALL were enrolled. One patient experienced significant toxicity in the form of hypotension, fever, rhabdomyolysis, hypophosphatemia and change in mental status 70 minutes after the BTZ infusion at the 1.3 mg/m^2 dose level. The drug was discontinued and the patient recovered from the toxicity. That cohort was then expanded at the same dose level of 1.3 mg/m^2 and no other patient experienced a similar toxicity. The phase II portion was recently reported at ASH 2011. Of the 22 patients enrolled on the study, 20 had B cell and 2 had T cell ALL. The overall response rate was 73% (14 CR and 2 CRp). The 2 patients with T cell ALL did not respond. Two patients developed grade 3 or higher peripheral neuropathy. Three patients died on study from infectious complications [24,28]. Based on the very high response rate in the phase II study, the Children's Oncology Group (COG) has adopted this regimen as the current clinical trial for patients with relapsed ALL. However, the combination has not been evaluated in adults with relapsed refractory ALL. Given the high efficacy seen in children, it seems logical to evaluate VXLD + BTZ in adults. One concern in the VXLD+ BTZ regimen is the potential for peripheral neuropathy, as both vincristine and BTZ have a high incidence of peripheral neuropathy.

Similar synergism between chemotherapy and other second generation proteosome inhibitors such as carfilzomib and ixazomib is observed in vitro in multiple myeloma [29,30] and lymphoma cells [31].

Ixazomib has a shorter proteosome dissociation half-life and improved antitumor activity when compared to BTZ [32]. Additionally, there were no grade 3 peripheral neuropathy events reported in the phase I or II trials [1,3,5]. The previous protocol version proposed combining a modified VXLD regimen with oral ixazomib for the treatment of adults with relapsed/refractory ALL. The modification was a reduction in pegaspargase administration frequency from weekly to every other week. The reason for this is twofold: 1) Adequate asparagine depletion can be achieved by a every 2 week schedule with pegaspargase [33]; and, 2) adults have poorer tolerance to asparaginase compounds in general[34].

Of the three patients enrolled on the VXLD + ixazomib protocol (previous version of this protocol), one patient had a grade 5 hyperbilirubinemia, one had a grade 4 hyperbilirubinemia and the third patient had grade 3 hyperbilirubinemia. Hyperbilirubinemia was attributed to pegaspargase. One patient achieved complete remission. All three patients were at the 2.3 mg level. Based on that, this revised protocol was developed eliminating pegaspargase from the regimen due to poor tolerance. PEG aspargase is known to have a grade 3-4 liver toxicity in 30- 50% of patients[35,36]. The toxicity is much more common in adults than in children. In one study[35], Grade 3/4 hyperbilirubinemia occurred in 31% of patients . Patients with grade 3/4 hyperbilirubinemia were older than those without hepatotoxicity (median age 39 vs 31 years). Grade 3/4 hepatotoxicity was long, with a median duration of 34 days to return to grade 1 for bilirubin and 38 days to return to grade 2 for transaminitis. Based on this the toxicities were expected.

In contrast hepatic failure or hyperbilirubinemia is an extremely rare event reported in patients receiving oral MLN9708 (please see IB attached)

In addition, more data has emerged suggesting that proteasome inhibition reverses glucocorticoid resistance. Therefore, the study postulates that by eliminating pegaspargase in this regimen we would maintain efficacy with reduced toxicity[8,37]. The VXD regimen (or VAD regimen) was evaluated in several trials both in the upfront and relapsed setting albeit older studies[38,39]. In the relapsed setting, 5 of 10 patients with relapsed ALL had a complete remission. In newly diagnosed patients, the complete remission rate was higher in patients < 60 years old compared to those older than 60 (60% vs. 90%) demonstrating that the combination of vincristine, anthracyclin and steroids is an effective regimen for patients with ALL.

Lymphoblastic lymphoma (LBL) and mixed phenotype acute leukemia (MPAL):

Lymphoblastic lymphoma is categorized in the same disease entity as ALL by the WHO[40]. Patients with LBL are treated with the same regimens utilized to treat ALL[41]. Therefore patients with the diagnosis of relapsed LBL will be included in the

study. MPAL is a rare type of leukemia where the blast cells express both myeloid and lymphoid markers[40]. Outcome of therapy is dismal in patients with MPAL. The CR rates range from 30-80% with a median disease free survival of 5-12 months and a median overall survival of 6.5-30 months[42]. Several retrospective studies have demonstrated that patients with MPAL have a better prognosis when treated with an ALL like regimen[42-45]. Based on that, patients with relapsed MPAL will be included on this study.

Table (2)

	VXLD	Modified VXLD	VXD
Drug	Day	Day	Day
Doxorubicin 60 mg/m^2	1	1	1
Vincristine 1.5 mg/ m^{2a}	1, 8, 15, 22	1, 8, 15, 22	1, 8, 15, 22
Pegaspargase 2500 IU/m^{2bc}	2, 8, 15, 22	2, 15	
Dexamethasone 10 mg/m^2	1-14	1-14	1-14
IT cytarabine 100 mg	1	1	1
IT methotrexate 12 mg	8 (CNS−)	8 (CNS−)	8 (CNS−)
Triple IT: -Methotrexate: 15 mg -Hydrocortisone: 15 mg -Cytarabine: 30 mg	8, 15, 22, (CNS+)	8, 15, 22, (CNS+)	8, 15, 22, (CNS+)

[a]Cap at 2 mg, [b] Cap at 3750 IU per dose, [c] PEG asparaginase 1000 IU/m^2 for patients > 55 years old

IT: Intrathecal. CNS +: Central nervous system involvement, CNS-: No CNS involvement

1.2 Ixazomib

1.3 Preclinical Experience

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

1.4 Clinical Experience

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapse/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, 2 phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with Revlimid and Dexamethasone (RevDex) versus placebo/RevDex. Both trials are combining ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies include evaluation of drug-drug interactions with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetic (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of NDMM are ongoing.

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting.

Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

1.5 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a median single-dose first time of occurance of maximum (peak) concentration (T_{max}) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days.[46] 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.[6] Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis. See the IB. Please refer to the current ixazomib IB and Safety Management Attachment (SMA) for information on the PK for IV doses of ixazomib.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that ixazomib is metabolized by multiple cytochrome enzymes P450 (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce drug-drug interactions (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 or inducer because of the potential for first-pass metabolism when ixazomib is administered via the PO route and because of

the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver microsomes. Ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

1.6 Clinical Trial Experience Using the Oral Formulation of ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma) have been treated in studies evaluating the oral ixazomib formulation. These patients have been treated with different doses of IXAZOMIB either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

Table 1-1 Clinical Studies of Oral ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO,TW, single agent	0.24-2.23 mg/m^2, TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28 day cycle	1.68-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23 mg/m^2) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A-42 day cycle) and W (Arm B-28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7mg, fixed dose, TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5 mg, fixed dose, W DLT: Esophageal ulcer, nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5 mg, fixed dose[a], W MTD: 4 mg DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N=64	PO, TW, combination with LenDex 21 day cycle	3.0-3.7 mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5 mg fixed dose[a] W
C16010 RRMM N = 1	PO, W, combination with LenDex	4.0 mg W

Table 1-1 Clinical Studies of Oral ixazomib

C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W
C16013 RRMM N = 9	PO, W, with LenDex	4.0 mg W
C16014 Symptomatic MM N=701	PO, combination with LenDex	ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=28	PO, combination with Dex	Part A: ixazomib 3.0 mg on Day 1 Part B: ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle
C16017 RR follicular lymphoma N=58	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45	Part A: PO, Day 1 of 15-day cycle Part B: PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
TB-MC010034 RRMM N = 10	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

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

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

a Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m^2 BSA dosing.

Overview of the Oral Formulation of ixazomib

The emerging safety profile indicates that oral IXAZOMIB is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral IXAZOMIB in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib 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 ixazomib Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-2 Summary of Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	Oral Single Agent Total N=201
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhoea	88 (44)
Vomiting	77 (38)
Constipation	46 (23)
Abdominal pain	33 (16)
General disorders and administration site conditions	151 (75)
Fatigue	103 (51)
Pyrexia	51 (25)
Oedema peripheral	27 (13)
Asthenia	31 (15)
Nervous system disorders	92 (46)
Headache	29 (14)
Dizziness	26 (13)

Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)
Decreased appetite	64 (32)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)
Anaemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash macular[a]	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnoea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

Source: ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

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

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens.

The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 1-3 Most Common (At Least 10% of Total) Treatment- Emergent Adverse Events in Oral Ixazomib Combination Studies

Primary System Organ Class Preferred Term	**Total Oral Combo Agent (5/6/8/13)** **n = 173** **n (%)**
Subjects with at Least One Adverse Event	**163 (94)**
Gastrointestinal disorders	**139 (80)**
Nausea	**65 (38)**
Diarrhoea	**81 (47)**
Vomiting	**51 (29)**
Constipation	**57 (33)**
General disorders and administration site conditions	**132 (76)**
Fatigue	**76 (44)**
Pyrexia	**39 (23)**
Oedema peripheral	**61 (35)**
Asthenia	**20 (12)**
Nervous system disorders	**115 (66)**
Headache	**28 (16)**
Dizziness	**34 (20)**
Neuropathy peripheral	**45 (26)**
Metabolism and nutrition disorders	**91 (53)**
Decreased appetite	**25 (14)**
Hypokalaemia	**34 (20)**
Blood and lymphatic system disorders	**88 (51)**
Thrombocytopenia	**49 (28)**
Anaemia	**45 (26)**
Neutropenia	**43 (25)**
Lymphopenia	**20 (12)**
Skin and subcutaneous tissue disorders	**102 (59)**
Rash maculopapulara	**29 (17)**
Rash maculara	**22 (13)**
Musculoskeletal and connective tissue disorders	**99 (57)**
Back pain	**42 (24)**
Pain in extremity	**31 (18)**
Arthralgia	**22 (13)**
Respiratory, thoracic and mediastinal disorders	**80 (46)**
Cough	**36 (21)**

Dyspnoea	**26 (15)**
Infections and infestations	**92 (53)**
Upper respiratory tract infection	**35 (20)**
Psychiatric disorders	**73 (42)**
Insomnia	**50 (29)**

Source: ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

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

Data from ongoing blinded pivotal trials (C16010) are not included.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

The clinical experience with ixazomib 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 ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors [3], non-Hodgkin's disease, Hodgkin's disease [4], relapsed and/or refractory multiple myeloma [RRMM; 5; 6], relapsed or refractory systemic light chain amyloidosis [RRAL; 7], and newly diagnosed multiple myeloma [NDMM; 8; 9; 10]) to date.

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

1.7 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involves 2 studies (C16003 and C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE.

Study C16003 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.(11, 12) Study C16004 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM.(13, 14, 15) Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

In the dose escalation component of both studies, patients had multiple myeloma that had relapsed following at least 2 lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were to be enrolled into 1 of 4 expansion cohorts, including a relapsed and refractory cohort, a carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a VELCADE-relapsed cohort.

Final study results are currently being analyzed, but preliminary data suggest that ixazomib has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated. Please refer to the ixazomib IB and SMA for further information.

1.8 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating ixazomib in combination with agents commonly used across treatment settings. The development of ixazomib in combination with lenalidomide with dexamethasone (LenDex) in patients with NDMM who are transplant eligible or ineligible involves 2 studies (C16005 and C16008) with similar study designs except for a few key differences, namely the schedules of ixazomib and dexamethasone. ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

All 3 studies are phase 1/2, with phase 1 focusing on safety and phase 2 on efficacy (and further characterization of safety). Please refer to the ixazomib IB and SMA for further information.

1.9 Clinical Trial Experience Using the Intravenous Formulation of ixazomib

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

1.10 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA.

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of ixazomib for the treatment of patients with advanced malignancy.

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

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective is to determine the maximum tolerated dose of IXAZOMIB with VXD and to assess the tolerability of VXD + ixazomib in adult patients with relapsed refractory acute lymphocytic leukemia/lymphoma, lymphoblastic lymphoma or mixed phenotype acute leukemia

2.2 Secondary Objectives

- To estimate the overall response rate (ORR) including both complete remission (CR) and complete remission with incomplete count recovery (CRi) with VXD + ixazomib

3. STUDY DESIGN

In this phase I study, escalating doses of ixazomib will be combined with a fixed dose VXD regimen. Ixazomib will be administered on day 1, 8, and 15. If the patient experiences a DLT the dose of MLN maybe reduced to the next dose level on day 8 or day 15 in that patient. DLT would be any grade 3 or more toxicity which is

thought to be probably or definitely related to ixazomib. Three patients will be treated per dose level unless dose limiting toxicity (DLT) is observed. The starting dose of ixazomib will be 2.3 mg orally on days 1, 8 and 15. If toxicity is seen at this level then dose may be reduced to 1.5 mg (dose level -1). If no DLT is seen in the first 3 patients, the dose will be increased to 3 mg and then to 4 mg orally on days 1, 8 and 15 in a classic 3 +3 phase I design. The study will not attempt to increase the dose beyond 4 mg orally which, if achieved with acceptable toxicity, would be accepted as the recommended phase 2 dose (RP2D). 0 of 3 DLTs would allow escalation to the next dose level. 1 of 3 DLTs will require expanding to six patients; 1 of 6 DLTs will allow escalation again. Two DLTs will require dose de-escalation. Given that the liver toxicity with the VXLD + ixazomib was attributed to pegaspargase and it is eliminated from this protocol, we will start at dose level 1 of 2.3 mg. The maximum tolerated dose (MTD) will be the highest dose administered at which no more than 1 DLT was observed. All patients will be evaluated for hematopoetic stem cell transplantation. If patients achieve CR and are eligible for HSCT, they will proceed to HSCT. If they are not eligible, no donor is identified or if HSCT will be delayed, and the patient has achieved benefit, then treatment may be repeated at the discretion of the investigator. A total of 9-18 patients will be enrolled on the study. The study duration will be about 2 years. The DLT observation period will be from first dose of MLN9708 to 28 days after the first dose. Dose escalation to a higher dose level will require the last patient on the previous dose level to be out of the DLT observation period.

Patients will be offered an opportunity to provide samples to the institutional bank for use in future research.

4. STUDY POPULATION

4.1 Inclusion Criteria

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

- Male or female patients 18 years or older
- Have relapsed B or T-precursor acute lymphocytic leukemia/lymphoma, lymphoblastic lymphoma or mixed phenotype acute leukemia with increased bone marrow or peripheral blood blasts by morphology with or without CNS involvement
- Prior therapy: At least two prior treatment attempts to induce remission with no limit on the number of prior treatment regimens.
- Patients are eligible after allogeneic stem cell transplantation
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Patients must meet the following clinical laboratory criteria:
    - Total bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN).
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN.
    - Calculated creatinine clearance $\geq$ 30 mL/min
    - Absolute neutrophil count (ANC) > 1,000/cmm and platelets > 75,000/cmm unless the cytopenias are secondary to disease
- Life expectancy reasonably adequate for evaluating the treatment effect
- Patients must be at least 2 weeks from major surgery, radiation therapy, participation in other investigational trials and have recovered from clinically significant toxicities of these prior treatments
- Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form 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 [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

- Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one 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 (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.).

4.2 Exclusion Criteria

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

- Patients who are Ph+ ALL who are naive to therapy with an approved tyrosine kinase inhibitor.
- Prior exposure to ≥350 mg/m2 of anthracycline (in doxorubicin equivalent dosing), or left ventricular fractional shortening less than 50%.
- Failure to have fully recovered (ie, ≤ Grade 2 toxicity) from the effects of prior chemotherapy regardless of the interval since last treatment.
- Major surgery within 14 days before enrollment.
- Chemotherapy in the last 14 days. (Steroids or Intrathecal chemotherapy will be allowed).
- Systemic treatment, within 7 days before study enrollment, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A

inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, or psychiatric illness/social situations that would limit compliance with study requirements. Patients receiving intravenous antibiotics for infections that are under control may be included in this study.
- Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
- Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or GI procedure that could interfere with the oral absorption or tolerance of treatment.
- Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
- Patient has ≥ Grade 2 peripheral neuropathy.
- Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
- Female patients who are breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

5. TREATMENT PLAN

All patients will start therapy within 4 weeks from the bone marrow biopsy.

Lumbar puncture with intrathecal chemotherapy will be performed on all patients on day 1 (+/-1 day) to evaluate for disease.

BM or peripheral blood blast will be collected for correlative studies (optional) prior to starting therapy. Details of therapy are as follows:

Vincristine 1.5 mg/m^2 to a maximum dose of 2 mg IV on days 1, 8, 15 and 22
Dexamethasone 10 mg/m^2 orally or intravenously on days 1-14
Doxorubicin 60 mg/m^2 on day 1 by IV bolus.

<u>For patients without CNS involvement:</u>
-Cytarabine 100 mg will be administered intrathecally on day 1 (+/-1 day) (cytarabine dose should be reduced to 50 mg if given through a central ommaya reservoir)
-Methotrexate 12 mg will be administered intrathecally on day 8 (+/-1 day)

<u>For patients with CNS involvement:</u>
-Cytarabine 100 mg will be administered intrathecally on day 1 (+/-1 day) (cytarabine dose should be reduced to 50 mg if given through a central ommaya reservoir)
-Triple intrathecal chemotherapy with cytarabine 30 mg, methotrexate 15 mg and hydrocortisone 15 mg on (Day 8, 15 and 22 (+/-1 day)).

A bone marrow biopsy/aspirate will be performed at D28 +\- 3 days. For patients in remission, and have an available donor for HCT should proceed to HCT and be removed from the protocol treatment. Patients will still be followed for survival and progression free survival. A second cycle of treatment may be administered at the investigators discretion.

Ixazomib will be administered orally once weekly on day 1, 8 and 15. The first 3 patients will receive 2.3 mg orally (dose level 1). Dose escalation or de-escalation

will then proceed as previously detailed. There will be no intrapatient dose escalation.

Table (7) Ixazomib dosing

	Day	Oral Dosing (mg)
Dose level -1	1, 8, 15	1.5
Dose level 1	1, 8, 15	2.3
Dose level 2	1, 8, 15	3
Dose level 3	1, 8, 15	4

Supportive care:

All patients will receive antibacterial, antiviral, antifungal and pnuemocystis carinii pneumonia (PCP) prophylaxis. Prophylaxis regimen may follow institutional guidelines. The following prophylaxis maybe used as guidelines:

Quinolones for antibacterial prophylaxis e.g., levofloxacin 500 mg orally daily

Antiviral prophylaxis: acyclovir 800 mg orally twice daily

Antifungal prophylaxis: Fluconazole 400 mg orally daily, or Liposomal Amphotericin B 9 mg/kg IV once per week or Caspofungin 50 mg IV /daily

PCP prophylaxis with SS bactrim daily, pentamidine inhalation 300 mg monthly, dapsone 100 mg daily or mepron

6. DRUG INFORMATION

6.1 Description of Investigational Agents (ixazomib)

Ixazomib Capsules

The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg and 2.0-, 0.5-, and 0.2 mg capsules as the active boronic acid. The different dose

strengths are differentiated by both capsule size and color as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink
2.0 mg	Size 2	Swedish orange
0.5 mg	Size 3	Dark green
0.2 mg	Size 4	White opaque

For additional details, please see the ixazomib IB.

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered 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 ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose.

6.2 Study Drug Administration

Ixazomib 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 subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 6.3).

Patients should be instructed to swallow ixazomib 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, except water) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. Followed by 8 ounces (240 mL) of water.

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

Ixazomib Destruction

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

Please refer to the Pharmacy Manual for additional instructions.

6.3 Doxorubicin

Source and Pharmacology: An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin induced

apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both. Doxorubicin serum decay pattern is multiphasic. The initial distributive t½ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal t½ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Formulation and Stability:

Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1], 150 mg[2] vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 75 mg[1], 200 mg[2] vials.

[1] Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF□(rapid dissolution formula) also contains methylparaben 1 mg per each 10 mg of doxorubicin to enhance dissolution.[2] Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.

Aqueous Solution:

Store refrigerated 2°-8°C (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection:

Store unreconstituted vial at room temperature 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free normal saline to

a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature under normal room light (100 footcandles) and 15 days under refrigeration 2°-8°C (36°-46°F). Protect from exposure to sunlight. Doxorubicin may be further diluted in 0.9%NaCl or dextrose containing solutions and administered by infusion.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol. Administer IV through the tubing of rapidly infusing solution of D5W or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

Supplier: Commercially available from various manufacturers. See package insert for further information.

Adverse effects

Cardiovascular:

Acute cardiotoxicity: Atrioventricular block, bradycardia, bundle branch block, ECG abnormalities, extrasystoles (atrial or ventricular), sinus tachycardia, ST-T wave changes, supraventricular tachycardia, tachyarrhythmia, ventricular tachycardia

Delayed cardiotoxicity: LVEF decreased, CHF (manifestations include ascites, cardiomegaly, dyspnea, edema, gallop rhythm, hepatomegaly, oliguria, pleural effusion, pulmonary edema, tachycardia); myocarditis, pericarditis

Central nervous system: Malaise

Dermatologic: Alopecia, itching, photosensitivity, radiation recall, rash; discoloration of saliva, sweat, or tears

Endocrine & metabolic: Amenorrhea, dehydration, infertility (may be temporary), hyperuricemia

Gastrointestinal: Abdominal pain, anorexia, colon necrosis, diarrhea, GI ulceration, mucositis, nausea, vomiting

Genitourinary: Discoloration of urine

Hematologic: Leukopenia/neutropenia (75%; nadir: 10-14 days; recovery: by day 21); thrombocytopenia and anemia

Local: Skin “flare” at injection site, urticaria

Neuromuscular & skeletal: Weakness

Postmarketing and/or case reports: Anaphylaxis, azoospermia, bilirubin increased, coma (when in combination with cisplatin or vincristine), conjunctivitis, fever, gonadal impairment (children), growth failure (prepubertal), hepatitis, hyperpigmentation (nail, skin & oral mucosa), infection, keratitis, lacrimation, myelodysplastic syndrome, neutropenic fever, neutropenic typhlitis, oligospermia, peripheral neurotoxicity (with intra-arterial doxorubicin), phlebosclerosis, radiation recall pneumonitis (children), secondary acute myelogenous leukemia, seizure (when in combination with cisplatin or vincristine), sepsis, shock, Stevens-Johnson syndrome, systemic hypersensitivity (including urticaria, pruritus, angioedema, dysphagia, and dyspnea), toxic epidermal necrolysis, transaminases increased, urticarial

Supportive Care:

Cardio Protective: Dexaroxane may be used and dosed per institutional standards

6.4 Vincristine

Source and Pharmacology: Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the

major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The P450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Formulation and Stability:

Vincristine is supplied in a vial each mL of which contains vincristine sulfate, 1 mg (1.08 µmol); mannitol, 100 mg; Sterile Water for Injection; acetic acid and sodium acetate are added for pH control. The pH of Vincristine Sulfate Injection, *USP* ranges from 3.5 to 5.5. This product is a sterile solution. Store refrigerated at 2°-8°C or 36°-46°F. Protect from light and retain in carton until time of use. Do not mix with any IV solutions other than those containing dextrose or saline.

Guidelines for Administration:

See Treatment and Dose Modifications sections of protocol.

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vincristine. The delivery of vincristine via either IV slow push or minibag is acceptable. Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

When dispensed the container or syringe containing vincristine must be enclosed in an overwrap bearing the statement "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

Supplier:

Commercially available from various manufacturers. See package insert for more detailed information.

Adverse Effects:

Cardiovascular: Edema, hyper-/hypotension, MI, myocardial ischemia

Central nervous system: Ataxia, coma, cranial nerve dysfunction (auditory damage, extraocular muscle impairment, laryngeal muscle impairment, paralysis, paresis, vestibular damage, vocal cord paralysis), dizziness, fever, headache, neurotoxicity (dose-related), neuropathic pain (common), seizure, vertigo

Dermatologic toxicity: Alopecia (common), rash

Endocrine & metabolic: Hyperuricemia, parotid pain, SIADH (rare)

Gastrointestinal: Abdominal cramps, abdominal pain, anorexia, constipation (common), diarrhea, intestinal necrosis, intestinal perforation, nausea, oral ulcers, paralytic ileus, vomiting, weight loss

Genitourinary: Bladder atony, dysuria, polyuria, urinary retention

Hematologic: Anemia (mild), leukopenia (mild), thrombocytopenia (mild), thrombotic thrombocytopenic purpura

Hepatic: Hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive liver disease)

Local: Phlebitis, tissue irritation/necrosis (if infiltrated)

Neuromuscular & skeletal: Back pain, bone pain, deep tendon reflex loss, difficulty walking, foot drop, gait changes, jaw pain, limb pain, motor difficulties, muscle wasting, myalgia, paralysis, paresthesia, peripheral neuropathy (common), sensorimotor dysfunction, sensory loss

Ocular: Cortical blindness (transient), nystagmus, optic atrophy with blindness

Otic: Deafness

Renal: Acute uric acid nephropathy, hemolytic uremic syndrome

Respiratory: Bronchospasm, dyspnea, pharyngeal pain

Miscellaneous: Allergic reactions (rare), anaphylaxis (rare), hypersensitivity (rare

6.5 Dexamethasone

Source and Pharmacology: Dexamethasone is a synthetic fluorinated glucocorticoid devoid of mineralocorticoid effects. Dexamethasone, 0.75 mg, has potent anti-inflammatory activity equivalent to approximately 5 mg of prednisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Elimination half-lives for the following age groups have been reported to be: infants and children under 2 years of age: 2.3 to 9.5 hours, 8 to 16 years: 2.82 to 7.5 hours, and adults (age not specified): 3 to 6 hours. The biologic half-life is 36- 72 hours. It is primarily metabolized in the liver and excreted by the kidneys.

Formulation and Stability:

Available in 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg tablets; liquid formulations are available in 0.5 mg/5 mL and 0.5 mg/0.5 mL concentration. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, and various dyes. Liquid formulations may include: 5%-30% alcohol, benzoic acid, sorbitol, sodium saccharin, glycerin, purified water, and various dyes. Dexamethasone Sodium Phosphate Solution for Injection is available as 4 mg/mL, 10 mg/mL, 20 mg/mL and 24 mg/mL. Four milligrams of dexamethasone sodium phosphate is equivalent to 3.33 mg of dexamethasone. Vial sizes include 1 mL, 5 mL, 10 mL, 25 mL, and 30 mL and are available in multi-dose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium and propyl paraben, benzyl alcohol, and EDTA.

Guidelines for Administration:

See Treatment and Dose Modifications section of the protocol.

Dexamethasone Sodium Phosphate for Injection may be given IV, or IM undiluted. For IV use, it may be further diluted in dextrose or saline containing solutions. Avoid benzyl alcohol containing dexamethasone solutions for use in neonates. Diluted solutions that contain no preservatives should be used within 24 hours, but maintain stability for at least 14 days in PVC bags at room temperature protected from light.

Supplier:

Commercially available from various manufacturers. See package insert for further information

Adverse effects:

Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, cardiomyopathy, CHF, circulatory collapse, edema, hypertension, myocardial rupture (post-MI), syncope, thromboembolism, vasculitis

Central nervous system: Depression, emotional instability, euphoria, headache, intracranial pressure increased, insomnia, malaise, mood swings, neuritis, personality changes, pseudotumor cerebri (usually following discontinuation), psychic disorders, seizure, vertigo

Dermatologic: Acne, allergic dermatitis, alopecia, angioedema, bruising, dry skin, erythema, fragile skin, hirsutism, hyper-/hypopigmentation, hypertrichosis, perianal pruritus (following I.V. injection), petechiae, rash, skin atrophy, skin test reaction impaired, striae, urticaria, wound healing impaired

Endocrine & metabolic: Adrenal suppression, carbohydrate tolerance decreased, Cushing's syndrome, diabetes mellitus, glucose intolerance decreased, growth suppression (children), hyperglycemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary-adrenal axis suppression, protein catabolism, sodium retention

Gastrointestinal: Abdominal distention, appetite increased, gastrointestinal hemorrhage, gastrointestinal perforation, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, weight gain

Genitourinary: Altered (increased or decreased) spermatogenesis

Hepatic: Hepatomegaly, transaminases increased

Local: Postinjection flare (intra-articular use), thrombophlebitis

Neuromuscular & skeletal: Arthropathy, aseptic necrosis (femoral and humoral heads), fractures, muscle mass loss, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents), neuropathy, osteoporosis, parasthesia, tendon rupture, vertebral compression fractures, weakness

Ocular: Cataracts, exophthalmos, glaucoma, intraocular pressure increased

Renal: Glucosuria

Respiratory: Pulmonary edema

Miscellaneous: Abnormal fat deposition, anaphylactoid reaction, anaphylaxis, avascular necrosis, diaphoresis, hiccups, hypersensitivity, impaired wound healing, infections, Kaposi's sarcoma, moon face, secondary malignancy

7. DOSE-MODIFICATION GUIDELINES

7.1 Recommended ixazomib Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

- Treatment with ixazomib will use a cycle length of 28 days.

All non-hematological toxicity considered to be related to treatment with ixazomib must have resolved to ≤ Grade 1, to the patient's baseline values, or to a level considered acceptable by the physician (eg, hypokalemia that can be managed by replacements) before the next dose of ixazomib could be given. There will be no dose modifications or delays for hematological toxicity as all patients will experience neutropenia and/or thrombocytopenia with the VXD regimen. In the pediatric study, Grade 3 or 4 neutropenia and thrombocytopenia occurred in 97.6 and 79.8% of patients treated with VXLD respectively.

Treatment modifications due to ixazomib-related AEs are outlined in Table (8 and 9).

Table (8) Ixazomib Treatment Modification (Delays, Reductions, and discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only[47]
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold study drug until resolution to Grade ≤ 1 or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)[47]
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold study drug until resolution to Grade ≤ 1 or baseline Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated[47]
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	

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

Table (9) Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities other than peripheral neuropathy)

Grade 3 nonhematologic toxicity judged to be related to ixazomib If not recovered to < Grade 1 or baseline in one week	• Hold study drug until resolution to Grade < 1 or baseline • Reduce study drug to next lower dose upon return to < Grade 1 or baseline	Symptomatic recommendations noted in Section 3.4
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

7.2 Dexamethasone

Hypertension: Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

Hyperglycemia: Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

Pancreatitis: Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and > Grade 3 amylase elevation (> 2.0x ULN).

Muscle Weakness: Dose may be reduced for grade 2 or 3 muscle weakness.

Osteonecrosis (ON, also referred to as avascular necrosis): Do not modify corticosteroid therapy for osteonecrosis during Induction or Delayed Intensification.

Varicella: Steroids should be held during active infection except during Induction. Do not hold during incubation period following exposure.

Inability to use oral doses:

For dexamethasone, substitute the IV preparation mg for mg.

Severe infection: Do not hold or discontinue steroids during Induction without serious consideration, as this is a critical period in the treatment of ALL.

Severe psychosis: Steroid dose may be decreased by 50% for severe psychosis.

7.3 Vincristine

Severe neuropathic pain (Grade 3 or greater): Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. NOTE: neuropathic pain can be not only severe but difficult to treat. However, since vincristine is an important component of curative therapy and the majority of neuropathies are ultimately reversible, vincristine therapy may be given at full dose at investigator discretion. Drugs such as gabapentin may be of value.

Vocal Cord paralysis: Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated.

Foot Drop, paresis: Should be Grade 3 to consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vincristine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure. Physical therapy may be beneficial to maintain range of motion and provide AFO’s and other forms of support. Drugs such as gabapentin may be of value.

Jaw pain: Treat with analgesics; do not modify vincristine dose.

Hyperbilirubinemia:

Direct bilirubin Dose reduction

< 3.1 mg/dL Full dose (maximum dose: 2 mg)

3.1-5.0 mg/dL 50% of calculated dose (maximum dose: 1 mg)

5.1-6.0 mg/dL 75% of calculated dose (maximum dose: 0.5 mg)

> 6 mg/dL Withhold dose and administer next scheduled dose if toxicity has resolved.

Do not make up missed doses.

Constipation or ileus (> Grade 3) or typhlitis: Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate resume at 50% of calculated dose (maximum dose: 1 mg) and escalate to full dose as tolerated.

Extravasation:

In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Suggestions below may be helpful but none are considered definitive:

1. Stop infusion, aspirate drug and blood if possible, remove needle.

2. Apply warm compress immediately for 1 hour then rotate on/off every 15 minutes for 24 hours.

3. Hyaluronidase 150 units/mL reconstituted with NS-inject 1 mL for each 1 mL of drug

extravasated.

7.4 Criteria for Beginning a Subsequent Treatment Cycle for IT

- Platelets >30 cmm
- Fibrinogen >100 mg/dL

7.5 Criteria for Toxicity Recovery for a New Cycle of Therapy to Begin:

- Absolute neutrophil count (ANC) > 1,000/cmm and platelets > 75,000/cmm unless the cytopenias are secondary to disease
- All other nonhematologic toxicity (except for alopecia) must have resolved to ≤Grade 1 or to the patient's baseline condition.

If the patient fails to meet the above criteria for retreatment, hold treatment. The patient should be re-evaluated weekly or more frequently to determine whether the criteria for retreatment have been met and a new cycle can begin. If the criteria for retreatment have been met refer to the appropriate drug modification guidelines to resume therapy.

8. 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 drug-drug interaction [DDI] with a strong inhibitor would increase ixazomib exposure and could lead to a higher probability of an AE.):

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

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient's use (Rationale: Unlike with inhibitors, if there were to be a DDI with an inducer, ixazomib exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib):

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

- Excluded foods and dietary supplements include St John's wort and Ginkgo biloba are not permitted.

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against ALL other than study drugs in this treatment regimen.

- Radiation therapy (note that in general, the requirement for local radiation therapy generally indicates disease progression).

- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day.

- Adjuvant hormone therapy for breast or prostate cancer

8.1 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.

- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.

- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoetin) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Millennium Clinical or Medical Representative. Erythropoietin will be

allowed in this study. Their use should follow published guidelines and/or institutional practice.

- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.

- Antiviral therapy such as acyclovir may be administered if medically appropriate.

- Concomitant treatment with bisphosphonates will be permitted, as appropriate.

- Patients who experience worsening neuropathy from baseline may be observed for recovery and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

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

9. PRECAUTIONS AND RESTRICTIONS

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

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

10. PREGNANCY

It is not known what effects ixazomib 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:

- 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 from the time of signing of the informed consent form through 3 months 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 [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

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

- 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 (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

11. PACKAGING AND LABELING OF IXAZOMIB

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

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

11.1 Storage, Handling, and Accountability for ixazomib

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

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

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

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

12. 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.

13. 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.

14. STATISTICAL AND QUANTITATIVE ANALYSES

14.1 Statistical Methods

This phase I trial will use a standard dose-escalation scheme involving cohorts of three patients without intra-patient dose escalation. A total of 9-18 patients will be enrolled to determine the safety of ixazomib with fixed VXD. Adverse events will be summarized with descriptive statistics at each dose level of ixazomib. Objective response will be summarized by dose level and overall with descriptive statistics such as the objective response rate with a 95% confidence interval.

15. ADVERSE EVENTS

15.1 Definitions

15.1.1 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.

15.1.2 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.

15.1.3 Serious Adverse Event Definition

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

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug

abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

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.

15.2 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 first dose of study drug through 30 days after administration of the last dose of IXAZOMIB. Any SAE that occurs at any time after completion of IXAZOMIB treatment or after the designated follow-up period 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 Ehab Atallah, 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 in English to Millennium Pharmacovigilance (or designee):

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

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The sponsor-investigator must fax or email 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 events (s): Sponsor-investigator's or sub-investigator's determination of 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 events(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 products(s), including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of such communication.

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

Suggested Reporting Form:

- SAE Report Form (a sample is provided by Millennium)
- US FDA MedWatch 3500A:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

- Any other form deemed appropriate by the sponsor-investigator

15.3 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 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 by Millennium)

16. ADMINISTRATIVE REQUIREMENTS

16.1 Data and Safety Monitoring

The Medical College of Wisconsin Cancer Center Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all cancer center investigator initiated clinical trials. A six to 8 member Data and Safety Monitoring Committee will complete a review of protocol-specific data safety monitoring reports, to provide recommendations on trial continuation, suspension or termination. The DSMC will review these reports no less than bi-annually. A summary of the DSMC activities are as follows

- Review the clinical trials for data integrity and safety
- Review all adverse events requiring expedited reporting as defined per protocol
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

DSMC will review each new patient entry following induction. The study should not enroll any additional patients until the DSMC reviews the current patient report, and after the patient has completed the DLT observation period. The DLT observation period will be from first dose of MLN9708 to 28 days after the last dose. Dose escalation to a higher dose level will require the last patient on the previous dose level to be out of the DLT observation period.

16.2 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 Millennium Pharmacovigilance(refer to Section 8.2).

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18. APPENDICES

18.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[48]

18.2 Response Criteria

CR—M1 (<5% blasts) bone marrow with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral counts (absolute neutrophil count (ANC) >750/µl and platelet count >75,000/µl).

CR without platelet recovery (CRp), M1 bone marrow with no circulating blasts or extramedullary disease and recovery of ANC >750/µl, but insufficient recovery of platelets (<75,000/µl);

Partial remission (PR), complete disappearance of circulating blasts and achievement of M2 (5–25% blasts) marrow status, without new sites of extramedullary disease, and with recovery of absolute neutrophil counts (ANC >750/µl)

Stable disease (SD), does not satisfy the criterion for PD, or has recovery of ANC >750/µl but fails to qualify for CR, CRp, or PR;

Progressive disease (PD), an increase of at least 25% in the absolute number of circulating leukemic cells, development of new sites of extramedullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets.

[i]