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A Phase I-II Trial of DA-EPOCH-R Plus Ixazomib as Frontline Therapy for Patients with MYC-aberrant Lymphoid Malignancies: The DACIPHOR Regimen

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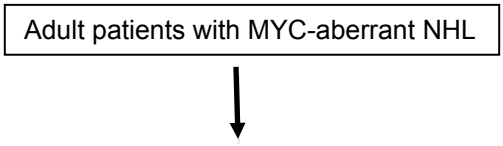
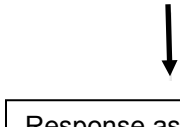
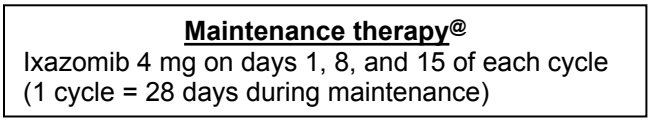
SCHEMA



Induction Therapy (6 cycles# of DA-EPOCH-R + Ixazomib)			
Drug	**Dose**	**Route**	**Schedule**
Etoposide	50 mg/m2/day	Continuous IV infusion	Days 1-4
Prednisone	60mg/m2/BID	PO	Days 1-5
Vincristine	0.4 mg/m2/day	Continuous IV infusion	Days 1-4
Doxorubicin	10 mg/m2/day	Continuous IV infusion	Days 1-4
Cyclophosphamide	750 mg/m2	IV (over 90 min)	Day 5
Rituximab	375 mg/m2	IV	Day 1**
Methotrexate	12 mg	Intrathecally	Once per cycle*
Ixazomib	variable^	Orally	Day 1 & Day 8 OR 15

*Due to high risk of CNS involvement, *all* patients will undergo diagnostic LP before or during their first treatment with DA-EPOCH-R, and if negative, IT methotrexate may be given per physician's preference using institutional guidelines.
^Dose will depend on which cohort/phase patient is enrolled to – starting dose is 2.3 mg.
#1 cycle = 21 days during induction
**For select institutions, rituximab may be given outpatient 1 to 3 days prior to scheduled cycle Day 1 as per institutional standard of care on any cycle; for cycle 1, if urgent chemotherapy administration is warranted, rituximab may be given following the first cycle of EPOCH therapy on any day prior to start of cycle 2.





@Maintenance therapy will be given to patients not treated with consolidative Stem Cell Transplant (SCT) for up to one year (if a patient is receiving clinical benefit after this period, an extension of ixazomib can be considered with documented approval from Takeda, the study PI and NU DSMC).

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate Aminotransferase
ATD	Accelerated titration design
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
COO	Cell of origin
CR	Complete Response
CT	Computed Tomography
CTO	Clinical Trials Office
CTCAE	Common Terminology Criteria for Adverse Events
DA-EPOCH-R	Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab
DHL	Double-Hit Lymphoma
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FISH	Fluorescent in-situ hybridization
GCB	Germinal Center B-cell
IHC	Immunohistochemistry
IT	Intrathecal
IV (or iv)	Intravenously
LP	Lumbar Puncture
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SCT	Stem cell transplant
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase

STUDY SUMMARY

Title	A Phase I-II Trial of DA-EPOCH-R Plus Ixazomib as Frontline Therapy for Patients with MYC-aberrant Lymphoid Malignancies: The DACIPHOR Regimen
Version	January 16, 2020 (Amendment 8)
Study Design	Phase I-II, multicenter, open-label. Phase I dosing will consist of dose finding with contingent dose de-escalation only if needed; phase II will then commence based on the RP2D identified by phase I. Phase II will be an Optimal Two-Stage design.
Study Center(s)	Northwestern University (Lead Site) Tufts University Cleveland Clinic Medical College of Wisconsin Rutgers Cancer Institute of New Jersey
Objectives	Primary (phase I): To evaluate the safety of ixazomib given with DA-EPOCH-R in patients with aggressive, MYC-aberrant lymphoid malignancies, and to determine the recommended phase II dose (RP2D) of the combination. Primary (phase II): To evaluate the efficacy, as measured by 12-month PFS, of ixazomib given with DA-EPOCH-R in patients with aggressive, MYC-aberrant lymphoid malignancies. Secondary objectives: 1. To further evaluate the frequency and severity of toxicity. 2. To further evaluate the clinical efficacy, as measured by RR and OS. 3. Assess predictive value of early FDG-PET/CT scans on PFS. 4. Assess the feasibility and outcomes of consolidation SCT.
Sample Size	Phase I: 3-9 patients Phase II: 37-46 patients
Diagnosis & Key Eligibility Criteria	Adult patients with MYC-aberrant non-Hodgkin lymphoma (NHL).
Treatment Plan	Ixazomib will be given in conjunction with 6 cycles of DA-EPOCH-R. In patients not treated with consolidative SCT, ixazomib will continue as maintenance for up to one year (or longer for continued clinical benefit with documented approval from Takeda, the PI, and DSMC).

Statistical Methodology	We expect to enroll 3-9 patients in phase I, and do not plan formal statistical analysis of these patients (although there will be a combined analysis for all patients in both phases for secondary endpoints). With respect to efficacy, our null hypothesis is that DA-EPOCH-R plus ixazomib will yield no difference in one-year PFS as compared to that observed in DHL, a rate we estimate at 40% based upon historical controls 1. We believe that the combination of DA-EPOCH-R plus ixazomib will warrant further validation if we can demonstrate improvement in one-year PFS by approximately 20%, to a rate of 60%. We therefore propose an Optimal Two-Stage Design to test the null hypothesis that P</=0.40 versus the alternative that P>=0.60, where P represents one-year PFS. We propose error probability limits of $\alpha>0.05$ and $\beta<0.20$. The Optimal Two-Stage Design provides for early stoppage of the trial if there is sufficient indication of futility 2. Under these conditions, if 7 or fewer of the first 16 patients are alive and progression-free at one year, the trial will be terminated, and DA-EPOCH-R plus ixazomib considered as having no greater efficacy than previously-reported treatment regimens. However, if 8 or more patients are alive and progression-free, the trial will proceed, to a total enrollment of 46 patients. If the number responding at this point is less than or equal to 23, the combination will not be considered superior to previously-reported regimens. Enrollment/treatment on this trial will NOT be stopped for sake of interim analysis; if there is evidence of futility once a sufficient number of patients have reached one year, any others enrolled before that time may continue per protocol. Patients from the first Phase who are treated at the MTD/RP2D and who are evaluable for response endpoints will be included in the Phase II efficacy analysis and will count towards total enrollment for Phase II.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

The human c-MYC oncogene is responsible for malignant transformation of several types of lymphoma, and is a sine qua non mutation associated with Burkitt Lymphoma (BL[3,4]). However, evidence of c-MYC rearrangement or over-expression is also found in up to ~20% of cases of Diffuse Large B-cell Lymphoma (DLBCL[5]), and in a recently-recognized provisional diagnostic category termed B-cell lymphoma, unclassifiable, with features intermediate between Diffuse Large B-cell and Burkitt Lymphoma (BCLU [6]).

There are various methods of detection of alterations in c-MYC, including fluorescent in-situ hybridization (FISH) for rearrangement; FISH for gain of copy number; and quantification of protein expression by immunohistochemistry (IHC). While the finding of translocation by FISH is universally recognized as evidence of clinically meaningful activation of c-MYC, the significance of gain of copy number, and degree of IHC positivity (including a cut-off for positive vs. negative), remains ill-defined in the literature [5,7].

Moreover, it has recently been recognized that other recurrent genetic translocations found in lymphoma, including BCL-2 and BCL-6, can co-occur with alterations in c-MYC, and subsequently confer particularly poor prognoses on patients whose tumors have these multiple mutations [7,8]. These so-called “double-hit lymphomas” (DHL) may represent over half of all cases of lymphoma with c-MYC mutations 7, and therefore would compose a substantial subset of cases of aggressive NHL.

1.1.1 Epidemiology

It is estimated that in 2010, there were 65,540 cases of NHL in the United States, and 20,210 deaths from the disease[9]. DLBCL is the most common sub-type of NHL, with approximately 20,000 new cases in the United States each year[9]. Chemo-immunotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) remains the standard first-line treatment, and high dose chemotherapy with rescue autologous stem cell transplant (ASCT) is generally the preferred second-line treatment[10]. However, in the rituximab era, the ability to salvage relapsed/refractory patients with an ASCT appears to be marginal, with efficacy further compromised in the subset of patients with a c-MYC aberration. Subsequently, approximately one-third of all patients with DLBCL will die due to disease relapse[11]. Therefore, additional treatment options are urgently needed.

Burkitt Lymphoma (BL) accounts for 1-2% of all lymphomas, with three recognized variants recognized: endemic [1]; sporadic [2]; and immunodeficiency-associated, which is generally observed in HIV+ patients [3].

1.1.2 Current Treatments

Since the introduction of rituximab and the advent of chemo-immunotherapy, R-CHOP has become the most widely utilized regimen for aggressive large cell lymphoma. While it can achieve a durable remission in approximately 60% of patients, recent retrospective analysis highlight this regimen’s marginalized efficacy in patients harboring a c-MYC mutation. There is little prospective data examining the utility of alternative induction regimens such as R-Hyper CVAD or DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab). However recently presented data analyzing a large cohort of patients with DHL suggests that DA-EPOCH-R may circumvent initial chemoresistance, offering a platform to build upon for treatment of c-MYC positive lymphoma’s.

With respect to Burkitt's Lymphoma, treatment was initially predicated upon combination regimens typically employed for acute lymphoblastic leukemia (ALL) consisting of induction, consolidation and maintenance phases. Subsequent modification to short-course, high-intensity regimens (e.g., Magrath and modified Magrath), seemed to improve upon survival compared to historical controls. On the other hand, less intensive anthracycline-based regimens, such as R-CHOP, effective for intermediate/aggressive lymphomas (including DLBCL]), are clearly inadequate for patients with BL, and yield poor results for patients with MYC-aberrant lymphoma and patients with DLBCL with IPI >/=3.

The successful deployment of risk adaptive approaches for patients with BL has led to a reduction in duration and intensity for many patients. Multi-agent chemotherapy regimens were developed, typically including anthracyclines, epipodophyllotoxins, vinca alkaloids, and alkylators, as well as methotrexate and cytarabine, which are cell cycle active agents and take advantage of the high tumor proliferation.

In order to mitigate risks of tumor lysis syndrome (TLS), some regimens (from French Society of Pediatric Oncology (SFOP), German Multicenter ALL Group (GMALL), and BFM), have employed a pre-treatment with low dose cyclophosphamide and prednisone. However, neither CODOX-M, Hyper-CVAD, nor DA-EPOCH-R, incorporate this pre-treatment strategy, and with appropriate precautions, have avoided significant rates of TLS. CNS involvement, and/or the high-risk thereof among patients with aggressive B-cell malignancies, has led to the use of high-dose intravenous methotrexate and cytarabine, both of which have CNS penetration, as well as intrathecal administration of both of these drugs. An important advance has been to reduce intrathecal treatment and eliminate whole brain radiation for prophylaxis, which has significantly reduced CNS toxicity.

1.2 Ixazomib

Ixazomib is an investigational, orally bioavailable, potent, reversible, specific inhibitor of the 20S proteasome that has demonstrated antitumor activity in in vivo models of multiple myeloma (MM) [19]. Safety, activity and pharmacokinetics (PK) of weekly oral ixazomib were recently reported in phase I trials in patients with relapsed and/or refractory NHL [14,20] and MM [21]. In these studies, patients received ixazomib at doses between 0.24–3.95 mg/m^2 (dose-escalation phase). MTD was not reached in the NHL trial, and was 2.97 mg/m^2 in the MM study. Common drug-related grade ≥3 adverse events were thrombocytopenia, diarrhea, neutropenia, decreased appetite, fatigue, and lymphopenia. Drug-related peripheral neuropathy was encountered, all grade 1-2. By investigator assessment in 41 evaluable MM pts, responses included 1 VGPR, 5 PR, 1 MR, and 15 with SD. In 16 evaluable patients with NHL, there were 3 PR and 4 SD.

Ixazomib was rapidly absorbed, with a terminal half-life of 4–12 days (supporting weekly dosing) and a proportional increase in plasma AUC with dose. PK data were similar across expansion cohorts. The authors of both studies concluded from that weekly oral ixazomib was generally well tolerated with infrequent peripheral neuropathy, and showed activity in heavily pretreated populations. A separate phase I/II study of the combination of ixazomib with lenalidomide and dexamethasone in untreated MM patients established the RP2D at 2.23 mg/m2, or a 4.0 mg flat dose [17]. A dose-escalation trial evaluating single-agent ixazomib in patients with relapsed/refractory NHL is now underway (ClinicalTrials.gov identifier NCT00893464), and multiple trials are now underway evaluating the agent in combination with IMIDs and/or glucocorticoids for the treatment of MM (http://clinicaltrials.gov/ct2/results?term=MLN9708). Accumulated data suggests that proteasome inhibition with bortezomib can be safely combined with intensive, anthracycline-based, combination chemotherapy in patients with untreated and

previously treated aggressive NHL, resulting in improved outcomes for those with DLBCL with non-GCB histology [22,23]. However, to our knowledge, no data has been reported for the combination of ixazomib with anthracycline-based therapy, nor are any such clinical trials currently underway.

1.2.1 Clinical Experience

Ixazomib (MLN9708) 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 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.

1.2.2 Pharmacokinetics and Drug Metabolism

After oral dosing, absorption of ixazomib is rapid with a median first time to maximum observed plasma concentration (Tmax) of approximately 1 hour postdose. The plasma exposure (AUC) of ixazomib increases in a dose-proportional manner over a dose range of 0.2 to 10.6 mg based on population PK analysis. The absolute oral bioavailability (F) of ixazomib is estimated to be 58% based on population PK analysis. A high-fat meal reduced ixazomib Cmax by 69% and AUC0 216 by 28%. This indicates that a high-fat meal decreases both the rate and extent of absorption of ixazomib. Therefore, ixazomib should be dosed at least 2 hours after food or 1 hour before food.

The steady-state volume of distribution of ixazomib is large and is estimated to be 543 L based on a population PK model. Based on in vitro plasma protein binding measurements on samples from clinical studies (Studies C16015 and C16018), ixazomib is highly bound to plasma proteins (99%). Ixazomib concentrations are higher in whole blood than in plasma, indicating extensive partitioning of ixazomib into red blood cells, which are known to contain high concentrations of the 20S proteasome.

Metabolism appears to be the major route of elimination for ixazomib. In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450 (CYP) and non-CYP proteins. At concentrations exceeding those observed clinically (10 μM), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (<1%). At 0.1 and 0.5 μM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, non-CYP proteins contribute to the clearance of ixazomib and no specific CYP isozyme predominantly contributes to the clearance of ixazomib. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor would be expected.

Ixazomib is neither a time-dependent inhibitor nor a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYPs 1A2, 2B6, and 3A4/5 activity or corresponding immunoreactive protein levels. Thus, the potential for ixazomib to produce DDIs via CYP isozyme induction or inhibition is low.

Ixazomib is not a substrate of BCRP, MRP2 and OATPs. Ixazomib is not an inhibitor of P gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2 K. Ixazomib is unlikely to cause or be susceptible to clinical DDIs with substrates or inhibitors of clinically relevant drug transporters.

The geometric mean terminal half-life (t1/2) of ixazomib is 9.5 days based on population PK analysis. For both IV and oral dosing, there is an approximately average 3 fold accumulation (based on AUC) following the Day 11 dose for the twice weekly schedule and a 2 fold accumulation (based on AUC) following the Day 15 dose for the once weekly schedule.

Mean plasma clearance (CL) of ixazomib is 1.86 L/hr based on the results of a population PK analysis. Taken together with the blood-to-plasma AUC ratio of approximately 10, it can be inferred that ixazomib is a low clearance drug. Using the absolute oral bioavailability (F) estimate of 58% (also from a population PK model), this translates to an apparent oral plasma clearance (CL/F) of 3.21 L/hr. The geometric mean renal clearance for ixazomib is 0.119 L/hr, which is 3.7% of CL/F and 6.4% of CL estimated in a population PK analysis. Therefore, renal clearance does not meaningfully contribute to ixazomib clearance in humans. Approximately 62% of the administered radioactivity in the ADME study (Study C16016) was recovered in the urine and 22% of the total radioactivity was recovered in the feces after oral administration. Only 3.2% of the administered ixazomib dose was recovered in the urine as unchanged ixazomib up to 168 hours after oral dosing, suggesting that most of the total radioactivity in urine was attributable to metabolites.

The PK of ixazomib was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor, and hence no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. Consistently, in a population PK analysis, co administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. Based on information from the clinical rifampin DDI study, ixazomib Cmax and AUC0-last were reduced in the presence of rifampin by approximately 54% and 74%, respectively. Therefore, the co-administration of strong CYP3A inducers with ixazomib is not recommended.

Mild or moderate renal impairment (CrCL ≥ 30 mL/min) did not alter the PK of ixazomib based on the results from a population PK analysis. As a result, no dose adjustment is required for patients with mild or moderate renal impairment. In a dedicated renal impairment study (C16015), unbound AUC0-last was 38% higher in patients with severe renal impairment or ESRD patients requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is appropriate in patients with severe renal impairment or ESRD requiring dialysis. Pre- and post-dialyzer concentrations of ixazomib measured during the hemodialysis session were similar, suggesting that ixazomib is not readily dialyzable, consistent with its high plasma protein binding (99%).

The PK of ixazomib is similar in patients with normal hepatic function and in patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (total bilirubin <1.5 times the upper limit of normal [ULN]), based on the results from a population PK analysis. Consequently, no dose adjustment is required for patients with mild hepatic impairment. In a dedicated PK study in patients with moderate (total bilirubin >1.5 to 3 times the ULN) or severe (total bilirubin >3 times the ULN) hepatic impairment (Study C16018), unbound dose-normalized AUC0-last was 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. Therefore, a reduced starting dose of ixazomib is appropriate in patients with moderate or severe hepatic impairment.

There was no statistically significant effect of age (23-91 years), sex, body surface area (1.2 2.7 m2), or race on the clearance of ixazomib based on the results from a population PK analysis.

Further details on these studies are provided in the IB.

1.2.3 Clinical Trial Experience with Oral Ixazomib

As of 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 Ongoing 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*: 4.0 mg fixed (switched to fixed dosing in phase 2, relevant 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]: 3-3.7 mg, 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 RR-AL N = 27	PO, W, single agent	4-5.5 mg, fixed dose[a], W 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 = 200	PO, W, combination with LenDex versus placebo- LenDex	4.0 mg fixed dose[a] W

Table 1-1 Ongoing 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.

1.2.4 Overview of Oral Formulation of Ixazomib

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

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of

146 patients have been treated as of April 2012. 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: Most Common (At Least 10% of Total) Treatment-Emergent AEs in Oral Single Agent Studies

Primary System Organ Class Preferred Term	Oral Single Agent Total n = 201 n (%)
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhea	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)
Edema 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)
Anemia	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)
Dyspnea	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 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 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)
Diarrhea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Edema 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)
Hypokalemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular[a]	29 (17)
Rash macular[a]	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)
Dyspnea	26 (15)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

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

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)

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[13], NHL and Hodgkin lymphoma[14], relapsed and/or refractory multiple myeloma [RRMM[15]], relapsed or refractory systemic light chain amyloidosis [RRAL[16]], and newly diagnosed multiple myeloma [NDMM[17,18]]) to date.

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

1.2.5 Relapsed and/or Refractory Multiple Myeloma (RRMM)

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. 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. 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.

1.2.6 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).

1.3 Rationale for the Current Study

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Takeda. 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. Therefore, we propose to conduct this phase I-II study to evaluate the incorporation of ixazomib into a DA-EPOCH-R backbone in adult patients with MYC-aberrant non-Hodgkin lymphoma (NHL).

The dosing schedule and regimen for dose adjusted EPOCH-R will follow established protocols. The dose of ixazomib will start at 2.3 mg weekly when given concurrently with DA-EPOCH-R. This dose is predicated on phase I data from patients with MM, wherein the recommended single-agent dose was established at 4 mg. Given the risk of overlapping hematological and neurological toxicity with concomitant cytotoxic and neurotoxic agents, the previous MTD was decreased by 50% for dosing cohort 1.

During phase I, an accelerated titration design (ATD) will be employed to more efficaciously determine the MTD of ixazomib in combination with DA-EPOCH-R. By this model [24], single-subject cohorts will be enrolled until the MTD is encountered, after which expansion to 3-subject cohorts will be undertaken. When used as single-agent maintenance, ixazomib will be dosed at 4mg weekly. The MTD will equate the RP2D for ixazomib in phase II. Phase II will be an Optimal Two-Stage design. Approximately 3-9 patients are anticipated for Phase I, and 46 patients for Phase II.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objectives/Endpoints

2.1.1 Phase I

The primary objective of the phase I portion will be to evaluate the safety of ixazomib given with DA-EPOCH-R in patients with aggressive, MYC-aberrant lymphoid malignancies, and to determine the recommended phase II dose (RP2D) of the combination.

The endpoint for this will be dose-limiting toxicity (DLT), defined as the occurrence of ≥ Grade 3 toxicity (using CTCAE v 4.03), experienced during the first cycle (3 weeks or 21 days) of study treatment, except for cytopenias. Grade 5 cytopenias will also be considered DLTs. The MTD will constitute the RP2D.

2.1.2 Phase II

The primary objective of the phase II portion will be to evaluate the efficacy, as measured by 12-month PFS, of ixazomib given with DA-EPOCH-R in patients with aggressive, MYC-aberrant lymphoid malignancies.

PFS will be defined as the time elapsed between treatment initiation and tumor progression or death from any cause, with censoring of patients who are lost to follow-up. The 12-month PFS will be defined as the percentage of patients alive and progression free 12 months from start of therapy.

2.2 Secondary Objectives/Endpoints

All secondary endpoints will consist of combined analysis of patients from both phase I and phase II.

2.2.1 Further evaluate the frequency and severity of toxicity.

Adverse events will be defined as those included in CTCAE v 4.03. The occurrence and severity of each will be recorded.

2.2.2 Further evaluate the clinical efficacy, as measured by response rate and OS.

Anti-tumor activity will be defined as the detection of SD, PR, or CR by CT or PET/CT, and/or resolution of marrow-only involvement. CR and PR will each be assessed according to the Revised Response Criteria for Malignant Lymphoma. Assessments will be performed after cycles 2 and 6, then at the discretion of the treating investigator.
OS will be defined as freedom from death by any cause.

2.2.3 Assess the predictive value of FDG-PET/CT scans on PFS.

Patients will be categorized as either FDG-PET (+) or (-) at interim and end-of treatment imaging.

2.3 Exploratory Objectives/Endpoints

2.3.1 Determine the impact of cell of origin (COO) upon response rate, PFS, and OS.

COO will be defined as GCB and non-GCB via the Hans algorithm (applicable only to patients with DLBCL).

2.3.2 Assess the feasibility and outcomes of consolidation SCT.

Patients will be grouped by whether consolidative SCT was performed in first remission, with PFS compared across groups (SCT vs. non-SCT).

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with MYC-aberrant NHL. This will be a multicenter trial conducted at Northwestern University, Tufts University, Cleveland Clinic, Medical College of Wisconsin, and Rutgers Cancer Institute. Northwestern University will serve as the lead site and coordinating center for this study.

A total of up to 54 subjects will be needed for this trial for this phase I/II trial (3-9 for phase I and up to 46 for phase II). Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Barbara Pro (312-695-4537), Dr. Andreas Klein at Tufts Medical Center (617-636-8227), Dr. Deepa Jagadeesh at Cleveland Clinic (216-444-0857) and Dr. Mehdi Hamadani at Medical College of Wisconsin, and Dr. Andrew Evens at Rutgers Cancer Institute.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a histological diagnosis of any of the following (all stages allowed):

- DLBCL (including transformation from a previously indolent NHL, so long as no prior systemic treatment was given for the indolent NHL)
- B-cell lymphoma, unclassifiable
- Burkitt lymphoma
- MYC+ plasmablastic lymphoma by histology.

NOTE: Histology must be CD20-positive, as measured according to standard institutional practice(s) for determining CD20 expression. CD20 positivity/expression must be clearly documented.

3.1.2 Patients must have measurable disease (defined as ≥ 1.5 cm in diameter).

3.1.3 Patients may have any of the following:

- MYC-overexpression (> 40%) by IHC;
- MYC-amplification (>4 copies), as determined by FISH
- MYC-rearrangement, as determined by FISH

3.1.4 The following results must be available or pending at time of registration, though results will not affect enrollment/treatment:

- BCL-2 rearrangement by FISH
- BCL-6 rearrangement by FISH

NOTE: Although not required, it is encouraged that MYC and BCL-2 be measured by immunohistochemistry (IHC) and clearly documented.

3.1.5 Patients must be age ≥ 18 years.

3.1.6 Patients must exhibit an ECOG performance status of 0-3.

3.1.7 Patients must meet the following clinical laboratory criteria:

- ANC ≥ 1,000/mm^3
- Platelets ≥ 75,000/mm^3
- Total bilirubin ≤ 1.5 x ULN
- AST(SGOT)/ALT(SPGT) ≤ 3 X institutional ULN
- Calculated creatinine clearance ≥ 30 mL/min

NOTE: ANC and platelet requirements do not apply to patients with marrow involvement of lymphoma (any extent).
NOTE: Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before registration.

NOTE: Exceptions can be granted from PI for instances of Gilbert's disease, and/or primarily indirect bilirubinemia, if due to recent transfusion and/or hemolysis.

3.1.8 Patients with HIV infection are eligible, provided they meet all of the following criteria:

- No history of AIDS-defining conditions or other HIV related illness
- CD4+ cells nadirs >350/mm^3 within 28 days prior to registration
- Treatment sensitive HIV and, if on anti-HIV therapy, HIV viral load < 50 copies/mm3 within 28 days prior to registration

3.1.9 Female patients must meet one of the following criteria:

- Postmenopausal for at least 1 year prior to registration
- Surgically sterile
- Of childbearing potential and agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 12 months after the last dose of study drug
- Of childbearing potential and agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject.

NOTE: periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.

3.1.10 Male patients, even if surgically sterilized (i.e., 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
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject.

NOTE: periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.

3.1.11 Females of childbearing potential (FOCBP) must have a negative pregnancy test within 7 days prior to registration on study.

3.1.12 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

3.2.1 Patients who have any prior chemoimmunotherapy are not eligible.

NOTE: The use of steroids to control the disease is permitted and does not have a washout period.

3.2.2 Patients who have had major surgery within 4 weeks prior to registration are not eligible.

3.2.3 Patients who have had radiotherapy within 14 days before registration are not eligible.

NOTE: If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.

3.2.4 Patients who have an infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment are not eligible.

3.2.5 Patients who have evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months are not eligible.

3.2.6 Patients who have undergone systemic treatment, within 14 days prior to registration, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort are not eligible.

3.2.7 Patients who have a clinically active hepatitis B or C virus infection are not eligible.

NOTE: Those with documented evidence of past exposure to HBV or HCV may enroll so long as the respective viral load is negative AND subject is willing/able to take appropriate antiviral prophylaxis to prevent reactivation; please refer to section 5.0 for baseline testing requirements.

3.2.8 Patients with any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol are not eligible.

3.2.9 Patients who have a known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent are not eligible.

3.2.10 Patients who have a known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing are not eligible.

3.2.11 Patients who have been 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 are not eligible.

NOTE: Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

3.2.12 Patients who have ≥ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period are not eligible.

3.2.13 Patients who are participating in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of registration and throughout the duration of this trial are not eligible.

3.2.14 Female patients who are nursing or have a positive pregnancy test during screening are not eligible.

4.0 TREATMENT PLAN

4.1 Overview

Ixazomib will be given in conjunction with 6 cycles of DA-EPOCH-R. During phase I, an accelerated titration design (ATD) will be employed to more efficaciously determine the MTD of ixazomib in combination with DA-EPOCH-R. The dosing schedule and regimen for dose adjusted EPOCH-R will follow established protocols. The dose of ixazomib will start at 2.3 mg weekly (for phase I patients) when given concurrently with DA-EPOCH-R. Single-subject cohorts will be enrolled until the MTD is encountered, after which expansion to 3-subject cohorts will be undertaken. The MTD from phase I will equate the RP2D for ixazomib given in conjunction with DA-EPOCH-R.

The MTD was established at cohort 2. As of August 10, 2016, all patients will be treated with ixazomib at 3mg during induction.

In patients who are not then treated with consolidative SCT, ixazomib will continue as maintenance for up to one year (if a patient is receiving clinical benefit after this period, an extension of ixazomib can be considered with documented approval from Takeda, the study PI and Northwestern University's Data and Safety Monitoring Committee (DSMC). When used as single-agent maintenance, ixazomib will be dosed at 4mg weekly.

NOTE: If a patient has dose reduced the ixazomib during the treatment phase (when it was given in combination with chemotherapy) and now enters the maintenance phase (where ixazomib will be administered as a single agent), the patient should start maintenance at the full dose of ixazomib (rechallenge at 4 mg weekly), not at the reduced dose; subsequent dose reductions may be considered if the patient does not tolerate the 4 mg dose during maintenance.

4.2 Treatment Schedule

4.2.1 Induction

Induction therapy will consist of 6 cycles of combination DA-EPOCH-R with ixazomib. During induction treatment, ixazomib will be given twice per cycle (1 cycle = 21 days during induction); the first dose will be given on day 1 and the second on either day 8 or 15. Based on existing experience with single-agent ixazomib, continuous weekly dosing without interruption can lead to toxicity. Therefore, during induction when ixazomib is administered with DA-EPOCH-R, ixazomib should be given on day 1, then as permitted by toxicity assessment on EITHER day 8 or 15, but not both. In other words, those who tolerate ixazomib dosing on day 1 and 8 of induction should NOT receive a dose on day 15, and those in whom day 8 ixazomib is held for toxicity can be given a day 15 dose if otherwise permitted by parameters of the trial.

In order to receive day 8 or 15 doses of ixazomib, patients must meet criteria specified below:

- ANC must be ≥ 1,000/mm3
- Platelet count must be ≥ 75,000/mm3
- All other non-hematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

4.2.2 Maintenance

Patients who do not go on to be treated with consolidative SCT will be treated with maintenance ixazomib for up to 1 year (or longer for continued clinical benefit with documented approval from Takeda, the PI, and DSMC. Similar to induction, maintenance with uninterrupted ixazomib may not be well-tolerated; therefore during maintenance treatment, ixazomib 4 mg will be given days 1, 8, and 15 of each cycle (1 cycle = 28 days during maintenance), and no drug will be given on day 22. *NOTE: If a patient has dose reduced the ixazomib during the treatment phase (when it was given in combination with chemotherapy) and now enters the maintenance phase (where ixazomib will be administered as a single agent), they should start maintenance at the full dose of ixazomib (rechallenge at 4 mg weekly), not at the reduced dose; subsequent dose reductions may be considered if the patient does not tolerate the 4 mg dose during maintenance.*

4.3 Treatment Administration

4.3.1 Ixazomib

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Capsules should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules. During induction, patients should take ixazomib in the hospital or clinic after labs have been assessed for toxicity on Day 1 and either Day 8 or 15 (see section 4.2.1). During maintenance, ixazomib will be dispensed on Day 1 of each cycle after labs have been assessed for toxicity. During the first two cycles of maintenance (Cycle 7 and 8), patients should have labs assessed before dosing on Day 8 and 15. Thereafter, Day 1 labs can be used for dosing on Day 1, 8, and 15.

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. Patients will be given a medication diary to keep track of all doses.

4.3.2 DA-EPOCH-R

Etoposide, vincristine, cyclophosphamide, doxorubicin, rituximab, and prednisone will all be obtained from commercial supply, and will be given per institutional guidelines for a total of 6 cycles of induction for all patients. For select institutions, rituximab may be given as an outpatient per institutional standard of care 1-3 days prior to the scheduled cycle day 1 for any cycle; for cycle 1, if urgent chemotherapy administration is warranted, rituximab may be given after the first cycle of EPOCH. All drugs will be given by IV route, except prednisone, which will be given orally (IV methylprednisolone may be substituted at discretion of treating investigator). The initial dosing cohort will consist of DA-EPOCH-R given in the standard fashion along with ixazomib at a starting dose of 2.3 mg (see 4.3.1 for ixazomib schedule). The DA-EPOCH-R regimen is summarized in the table below.

Table 4-1: DA-EPOCH-R Dosing Route & Schedule for Each Cycle of Induction

Drug	Dose	Route	Schedule
Etoposide	50 mg/m2/day	Continuous IV infusion	Days 1-4
Prednisone	60 mg/m2/BID	PO	Days 1-5*
Vincristine	0.4 mg/m2/day	Continuous IV infusion	Days 1-4
Doxorubicin	10 mg/m2/day	Continuous IV infusion	Days 1-4
Cyclophosphamide	750 mg/m2	IV (over 90 min)	Day 5
Rituximab	375 mg/m2	IV	Day 1**
Methotrexate	12 mg	Intrathecally	Once per cycle***

*Dosing schedule and administration for prednisone may vary if appropriate per institutional standards or physician discretion.

**For select institutions, rituximab may be given outpatient 1-3 days prior to the scheduled cycle day 1 per institutional standard of care for any cycle; for cycle 1, if urgent chemotherapy administration is warranted, rituximab may be given after the first cycle of EPOCH therapy on any day prior to start of cycle 2. In addition, if the Rituximab infusion is delayed for any reason and spans longer than one day, the dosing schedule can be adjusted appropriately.

*** Due to high risk of Central Nervous System (CNS) involvement, all patients will undergo diagnostic lumbar puncture (LP) per institutional standards before or during their first treatment with DA-EPOCH-R. If negative, IT methotrexate (or equivalent, see section 4.7) may be given per physician's preference using institutional guidelines.

All patients must receive either 1 dose of neulasta within 72 hours of completion of each cycle of DA-EPOCH-R, or must receive neupogen, 5mcg/kg (rounded to 300 mcg or 480 mcg) daily for 10 days starting within 72 hours of completion of each cycle of DA-EPOCH-R.

4.4 Dose Escalation Scheme – Phase I Induction Only

During Phase I, an accelerated titration design (ATD) will be employed to more efficaciously determine the MTD of ixazomib in combination with DA-EPOCH-R. The MTD will equate the RP2D for ixazomib in Phase II. Single-subject cohorts will be enrolled until MTD is encountered, after which expansion to 3-subject cohorts will be undertaken. The cohort-specific doses are provided in the table below.

Table 4-2: Dose Escalation Scheme for Induction – Phase I Only

Cohort	Ixazomib Dose (mg)	Days of Administration
1	2.3	1 and either 8 or 15
2	3	1 and either 8 or 15
3	4	1 and either 8 or 15

Dosing of ixazomib will not exceed 4 mg; if no DLTs are experienced at 2.3 mg and 3 mg single-patient cohorts, the 4 mg cohort will enroll 3 patients to evaluate for toxicity. If no

DLT are experienced among 3 patients at 4 mg, this will be declared the RP2D. If, however, 1 or more patients experiences DLT at the 4 mg cohort, an additional 2 patients will be treated at the 3 mg level (for 3 total patients at this dose level). If 1 or more patients at the 3 mg level experience DLT, an additional 2 patients will be treated at the 2.3 mg level (for 3 total patients at this dose level). Therefore, phase I will treat between 5 and 9 patients. If unacceptable toxicity is observed at 2.3mg dose, enrollment will be suspended for re-evaluation of dose-finding strategy.

MTD was established at cohort 2. As of August 10, 2016, all patients will be treated with ixazomib at 3mg during induction.

4.4.1 Dose Limiting Toxicities

Dose limiting toxicities will be defined as the occurrence of any ≥ Grade 3 drug-related toxicity (using CTCAE v 4.03), experienced during cycle 1 (the first 21 days) of study treatment, *except for cytopenias*. Since cytopenias are expected, particularly in later cycles, the omission of drug at day 8 and 15 for hematologic toxicity will not, by itself, be considered a DLT. However, grade 5 cytopenias will be considered DLTs.

4.5 Dose Modifications

4.5.1 Induction Chemotherapy Dose Modifications

Dose modifications for DA-EPOCH-R should be utilized as appropriate per standard practice for patients *outside the DLT evaluation window* during induction therapy. Doses may be delayed as clinically warranted up to 3 weeks, and patients do not need to come off study for dose delays during induction.

For occurrence of motor or sensory neuropathy during induction, see footnote c below for suggested modifications of vincristine.

Table 4-3: DA-EPOCH-R Dose Adjustments for Intra-Patient Dose Modification

	Dose Levels								
	-2	-1	1[a]	2	3	4	5	6	7
Adjusted Agents[a]									
Doxorubicin (mg/m^2/day)	10	10	10	12	14.4	17.3	20.7	24.8	29.8
Etoposide (mg/m^2/day)	50	50	50	60	72	86.4	103.7	124.4	149.3
Cyclophosphamide (mg/m^2/day)	480	600	750	900	1080	1296	1555	1866	2239
Non-Adjusted Agents									
Rituximab (mg/m^2)	375	375	375	375	375	375	375	375	375
Vincristine[b,c](mg/m^2/day)	0.4[b,c]	0.4[b,c]	0.4[b,c]	0.4[b,c]	0.4[b,c]	0.4[b,c]	0.4[b,c]	0.4[b,c]	0.4[b,c]
Prednisone[b] (mg/m^2 BID)	60[b]	60[b]	60[b]	60[b]	60[b]	60[b]	60[b]	60[b]	60[b]
Methotrexate[d] (mg)	12[d]	12[d]	12[d]	12[d]	12[d]	12[d]	12[d]	12[d]	12[d]
Ixazomib	MTD[e]	MTD[e]	MTD[e]	MTD[e]	MTD[e]	MTD[e]	MTD[e]	MTD[e]	MTD[e]

a. Level 1 is the starting dose for DA-EPOCH-R. Dose adjustments above starting dose level (level 1) apply to etoposide, doxorubicin and cyclophosphamide. Dose adjustments below starting dose level (level 1) apply to cyclophosphamide only.
b. The dose of prednisone and vincristine can be modified at the treating physician's discretion for older patients with poor tolerance.
c. It is suggested that the dose of vincristine is reduced 25% or 50% for grade 2 or 3 motor neuropathy, respectively, and reduced by 50% for grade 3 sensory neuropathy.
d. For CSF negative patients who are considered at high risk of CNS disease, intrathecal (IT) chemotherapy should be given per physician's preference using institutional guidelines.
e. The dose of ixazomib may be reduced for toxicities ≥Grade 3, other than cytopenias, after discussion with the PI. If ixazomib is interrupted for > 3 weeks, DSMC approval must be obtained in order for patients to resume treatment per Section 4.5.2.1.

Table 4-4: Criteria for Dose Adjustment of DA-EPOCH-R

ANC > 500/μL on all measurements	Increase 1 dose level
ANC < 500/μL on 1 or 2 measurements (3-4 days apart)	Maintain current dose level
ANC < 500/μL > 3 measurements (3-4 days apart)	Decrease 1 dose level
Platelets < 25,000 on > 1 measurement	Decrease 1 dose level

4.5.2 Dose Delays/Modifications for Ixazomib

4.5.2.1 Dose Delays (Induction and Maintenance)

Treatment with ixazomib will use a cycle length of 28 days (with scheduled doses on day 1 and either day 8 or 15 of induction, and days 1, 8, and 15 of each maintenance cycle). For a new cycle of treatment to begin during both induction and maintenance, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm3
- Platelet count must be ≥ 75,000/mm3
- All other non-hematologic 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-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate. The maximum delay before treatment should be permanently discontinued will be 3 weeks; however, delays of longer than 3 weeks may be considered on a case-by-case basis with notification to the QAM and upon receipt of DSMC approval.

Please refer to the Tables 4-5, 4-6, and 4-7 below for ixazomib dose delays and modifications during maintenance therapy for both hematologic and non-hematologic toxicities. NOTE: Once maintenance ixazomib is reduced for any toxicity, the dose may not be re-escalated.

Table 4-5: Ixazomib Dose Adjustments During Maintenance

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

*The starting dose for maintenance ixazomib will be 4.0 mg.

NOTE: If a patient has dose reduced the ixazomib during the treatment phase (when it was given in combination with chemotherapy) and now enters the maintenance phase (where ixazomib will be administered as a single agent), they should start maintenance at the full dose of ixazomib (rechallenge at 4 mg weekly), not at the reduced dose; subsequent dose reductions may be considered if the patient does not tolerate the 4 mg dose during maintenance.

Table 4-6: Ixazomib Dose Modifications for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count $\leq 30 \times 10^9$/L or ANC ≤ 0.50 $\times 10^9$/L on a ixazomib dosing day (other than Day 1)	• Ixazomib dose should be withheld. • CBC with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values (see above) on at least 2 occasions. • Upon recovery, ixazomib may be reinitiated at 1 dose level lower.
Dose Modifications for Subsequent Treatment Cycles	
• Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery (ANC < 1.0×10^9/L, platelet count < 75×10^9/L, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition)	• Hold ixazomib until resolution as per criteria above. • Upon recovery, reduce ixazomib by 1 dose level. • The maximum delay before treatment should be discontinued will be 3 (unless DSMC approved – see above).
Dose Modifications for Subsequent Treatment Cycles	

• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle,:
	  ○ If dose was reduced within the cycle, start the next cycle at that same dose.
	  ○ If due to toxicity timing, (i.e., after Day 15 dosing), reduce ixazomib by 1 dose level at the start of that next cycle.
	  ○ Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

Table 4-7: Ixazomib Dose Modifications for Non-Hematologic Toxicities

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy		
Grade 1 peripheral neuropathy	No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only
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)
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
New or worsening Grade 4 peripheral neuropathy	Discontinue study drug	N/A
Rash		
Grade 2 Rash	Symptomatic recommendations	May consider dose modifications and symptom management.
Grade 3 Rash	Reduce by 1 dose level.	
Other		
Grade 3 nonhematologic toxicity judged to be related to study drug If not recovered to < Grade 1 or baseline within 4 weeks	• Hold study drug until resolution to Grade < 1 or baseline • Reduce study drug 1 to next lower dose upon return to < Grade 1 or baseline	Symptomatic recommendations noted in Section 6.7
Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 4 weeks	• Hold study drug until resolution to Grade < 1 or baseline • Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 non hematologic 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

4.6 Concomitant Medications/Procedures

4.6.1 Required Concomitant Medications/Procedures

The following are required during induction therapy:

- Bactrim DS with dosing per institutional guidelines (or equivalent if allergic).
- Omeprazole 20 mg/day PO (or equivalent).
- Stimulant laxative/stool softener (e.g., Pericolace®) 2 tablets PO BID (adjusted as necessary) or institutional preference for prevention of constipation.
- Lactulose 20 g PO Q6 hours PRN until resolution or institutional preference for treatment of constipation.
- Acetaminophen 650 mg PO and diphenhydramine 50-100 mg IV or PO 30 to 60 minutes prior to starting each rituximab infusion.
- Hepatitis B & C surface Ag+ patients should receive lamivudine, entecavir, tenofovir or equivalent per institutional guidelines during therapy and until at least 12 weeks beyond completion of induction therapy.
- Fluid deficit should be corrected before initiation of treatment and during treatment.

4.6.2 Prohibited Concomitant Medications/Procedures

The following medications and procedures are prohibited during the study.

- Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use. A DDI with a strong inducer would decrease ixazomib exposure:
    - Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
    - The dietary supplements St John's wort and Ginkgo biloba are not permitted.
- The following procedures are prohibited during the study:
    - Any antineoplastic treatment with activity against lymphoma except for drugs in this treatment regimen.
    - Radiation therapy (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 registration.

4.6.3 Permitted Concomitant Medications/Procedures

The following medications and procedures are permitted during the study:

- **Antiemetics**, including 5-HT3 serotonin receptor antagonists, are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may be used at the discretion of the investigator (NOTE: dexamethasone should not be administered as an anti-emetic). Fluid deficit should be corrected before initiation of study drug and during treatment.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator (once infectious causes are excluded). The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The use of a **topical, IV, or oral steroid** (e.g., prednisone ≤ 10 mg per day or equivalent) is

permitted. Management of a Grade 3 rash may require **intravenous antihistamines or corticosteroids**.

- **Growth factors** (e.g., G-CSF, GM-CSF, recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Takeda 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.
- Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated. Other antivirals are also acceptable.
- 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.
- Steroids used to control a patient's lymphoma are permitted and have no washout prior to starting study treatment.

NOTE: Although no specifically prohibited, nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

4.7 CNS Prophylaxis and Treatment

Due to high risk of CNS involvement, all patients will undergo diagnostic Lumbar Puncture (LP) before or during the first cycle of DA-EPOCH-R, and if negative, IT methotrexate may be given per treating physician's preference using institutional standards. If the CSF is cytologically positive at the time CNS prophylaxis is scheduled to begin, the patient should receive active treatment of the CSF with methotrexate per institutional standards.

4.8 Supportive Care

4.8.1 Reactivation of Herpes Infection

Please see 4.6.3 for permitted therapies.

4.8.2 Nausea and/or Vomiting

Please see 4.6.3 for permitted therapies. Fluid deficit should be corrected before initiation of study drug and during treatment.

4.8.3 Diarrhea

Please see 4.6.3 for permitted therapies.

4.8.4 Erythematous Rash with or without Pruritus

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on

the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

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

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (e.g., using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare risk is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

4.8.5 Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

4.8.6 Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice (see above). Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs. Therapy can be reinitiated at a reduced level upon recovery of ANCs.

4.8.7 Antibiotic Prophylaxis

Antibiotic prophylactic medications are permitted and encouraged during study treatment. Regimens should follow institutional standards. Recommendations include:

- Bactrim® DS twice daily Monday, Wednesday, Friday
- Acyclovir 400mg once daily
- Fluconazole 100mg once daily

4.8.8 Fluid Deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

4.8.9 Hypotension

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

4.8.10 Posterior Reversible Encephalopathy Syndrome

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

4.8.11 Transverse Myelitis

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

4.9 Duration of Therapy & Follow-Up

Study treatment will include induction therapy (6 cycles of 21 days each) followed by up to 1 year of maintenance therapy (1 cycle = 28 days during maintenance). In the absence of treatment delays due to adverse events, maintenance treatment may continue for up to one year or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

During follow-up, patients will be followed with at least one clinic visit every three months, for one year after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.10 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety,

behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

4.11 Replacement of Subjects

Subjects who receive at least 1 dose of investigational treatment are evaluable for toxicity. However, should a patient come off treatment within the DLT period for any reason other than a DLT (e.g. patient refusal, unrelated adverse event), an additional patient may be added to the cohort at the discretion of the QAM and DSMC.

5.0 STUDY PROCEDURES

Table 5-1: Study Procedures

	Screening	On Treatment					Off Treatment	
Time Period	Baseline[10]	Induction (C1-6)[7]		Maintenance (C7+)[7]			Off Treatment[15]	Follow-up[9]
		Day 1 (± 3 days)	Day 8, 15 (± 3 days)	Day 1 (± 3 days)	Day 8 (± 3 days)	Day 15 (± 3 days)		
Assessment or Activity								
Informed Consent	X							
Medical history	X							
Physical exam[1]	X	X[1]		X				X
ECOG status	X	X[1]		X			X	
Concomitant medications	X	X		X			X	
Toxicity assessment	X	X	X	X			X	
Disease Assessment[2]	X	X[2]		X[2]			X	X
CBC with diff[4]	X[4]	X	X[4]	X	X	X		
Chemistry panel[4]	X[4]	X	X[4]	X	X	X		
Pregnancy test[3]	X							
Hep B & C screen[11]	X[11]							
MYC and BCL2 status by FISH and IHC[5, 6]	X[10]							
Peripheral blood banking[8]		X[8]		X[8]				
Lumbar Puncture[12]	X	X[12]						
DA-EPOCH-R administration[13]		X						
Ixazomib administration[14]		X	X[14]	X	X	X		

[1] Includes vital signs (pulse, blood pressure) and height (baseline only) and weight. Physical exam and ECOG PS do not need to be repeated at C1D1 if performed as part of screening within 7 days prior.

[2] Tumor assessment will be by means of PET/CT at baseline, after cycle 2 of induction (within 7 days of the start of cycle 3), and at the "Off Treatment" visit. Tumor assessments will also occur after induction (within 2 weeks of starting maintenance) and every 6 months thereafter and may consist of PET/CT or CT alone at the treating investigator's discretion. Patients who are unable to get PET imaging for any reason will NOT be precluded from participation. While diagnostic-quality CT is encouraged, it is not required.

[3] Serum test for females of child-bearing potential is required within 7days prior to registration.

[4] Patients will have CBC with differential and Chemistry panel drawn at screening (≤14 days from registration) as well as prior to dosing at each study visit. Labs are not required at time points where dosing does not take place (for example, if a patient receives ixazomib day 8 and not day 15, labs are not required on day 15; labs are not required for patients who discontinue therapy prior to the maintenance period).

[5] Patients MUST have a tumor that is MYC+ by FISH or IHC for enrollment, but other results may be pending and are not required to for eligibility/registration purposes.

[6] FISH status for all patients and for all three markers (MYC, BCL2, and BCL6) should be reported as +/- for translocation (aka rearrangement), and if negative for translocation, by any reported gain of copy number or amplification (including number of copies for MYC translocation). IHC is preferred but not required for enrollment.

[7] During induction, one cycle = 3 weeks or 21 days; during maintenance, one cycle = 4 weeks or 28 days. For patients who do not receive SCT, maintenance will begin after C6 (Cycle 7 will start at Cycle 6 Day 22 +/- 7 days) and will consist of ixazomib treatment on Days 1, 8 and 15 of each cycle for up to 1 year from the start of Cycle 7. If a patient is receiving clinical benefit after this period, an extension of ixazomib treatment can be considered with documented approval from Takeda, the PI, and DSMC.

[8] Phase II patients, only if patient agrees to optional blood draws: One red top tube and one green top tube will be drawn on day 1 of induction cycles 1 & 2, and day 1 of the first 3 maintenance cycles. Blood will be frozen and stored in the Biorepository of the Pathology Core Facility at Northwestern University for future, unspecified use.

[9] Patients will be followed with at least one clinic visit every three months, for one year after removal from treatment or until death, whichever occurs first, to document disease progression and survival status. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event

[10] Screening assessments must be completed within 28 days prior to registration (with the exception of labs, which must be within 14 days, FISH and IHC, which may be assessed within an indefinite window, and Hepatitis B & C which may be within 42 days).

[11] Patients must have baseline HBV surface Ag and HCV ab at a minimum ≤ 42 days (6 weeks) prior to registration. If either is positive, patients should have viral load of the corresponding infection (HBV or HCV) documented. NOTE: patients who are HBV surface Ag+ MUST agree to treatment/prophylaxis with appropriate antiviral therapy in order to be enrolled.

[12] All patients should have a lumbar puncture (LP) per institutional standards before or during the first cycle of DA-EPOCH-R. Additional lumbar punctures will then be performed following the standard of care and treating physician's discretion. The initial LP will determine a patient's CNS involvement to dictate the recommended prophylactic treatment with methotrexate (see section 4.7)

[13] DA-EPOCH-R will be administered Day 1-5 of each cycle during induction (a total of 6 cycles). See section 4.3.2 for treatment and dosing details as well instructions on methotrexate administration. The DA-EPOCH-R regimen will follow institutional standards and details are provided in the protocol for convenience.

[14] Ixazomib is an oral pill that will be administered on Day 1 and either Day 8 or Day 15 of each cycle during induction (see section 4.2.1 for laboratory requirements). Day 8 dosing should be administered unless held for toxicities, in which case, patients should be re-challenged on Day 15. During Phase I, each patient's dose will depend on the cohort assignment (either 2.3mg, 3mg, or 4mg). During Phase II, all patients will be dosed at the MTD determined during Phase I. Once a patient has completed 6 cycles of induction, he or she may continue maintenance therapy with ixazomib alone on days 1, 8, and 15 of each cycle for up to one year. Maintenance dosing will begin at a standard dose of 4mg for all patients. See Table 4-5 for permitted dose modifications during the maintenance phase.

[15] An end of treatment visit will occur 21 days after the last study treatment (+/- 7 days)[16] During the first 2 cycles of maintenance therapy (Cycle 7 and 8), labs should be assessed weekly prior to ixazomib dosing. Thereafter, labs from Day 1 of each cycle can be used for dosing on Day 1, 8 and 15.

6.0 ENDPOINT ASSESSMENT

Patients must complete at least 2 cycles of induction therapy and undergo a subsequent disease response assessment to be evaluable for response endpoints; patients who complete less than 2 cycles will be evaluable for toxicity endpoints only.

6.1 Primary Endpoints

The primary endpoint for the phase I portion of the study will be dose-limiting toxicity (DLT), defined as the occurrence of ≥ Grade 3 toxicity (using CTCAE v 4.03), experienced during the first cycle (3 weeks or 21 days) of study treatment, except for cytopenias. Grade 5 cytopenias will also be considered DLTs. All patients who receive at least one dose of ixazomib will be evaluable for this endpoint.

The primary endpoint of the phase II portion will be 12-month PFS. PFS will be defined as the time elapsed between treatment initiation and tumor progression or death from any cause, with censoring of patients who are lost to follow-up. The 12-month PFS will be defined as the percentage of patients alive and progression free 12 months from start of therapy.

6.2 Secondary Endpoints

All secondary endpoints will consist of combined analysis of patients from both phase I and phase II.

Adverse events will be defined as those included in CTCAE v 4.03. The occurrence and severity of each will be recorded. Responses will be determined by categorizing patients as SD, PR, or CR by CT or PET/CT, and/or resolution of marrow-only involvement. CR and PR will each be assessed according to the Revised Response Criteria for Malignant Lymphoma (see definitions in section 6.4 below). Assessments will be performed after cycle 2 and after induction therapy (prior to start of maintenance therapy), and then at the discretion of the treating investigator. OS will be defined as freedom from death by any cause. To assess the predictive value of FDG-PET/CT scans on PFS, patients will be categorized as either FDG-PET (+) or (-) at interim and end-of-treatment imaging.

6.3 Exploratory Endpoints

Cell of origin (COO) will be defined as GCB and non-GCB via the Hans algorithm (applicable only to patients with DLBCL). These results will be correlated with response rate, PFS, and OS. Patients will be grouped by whether consolidative SCT was performed in first remission, with PFS compared across groups (SCT vs. non-SCT), in order to assess the feasibility and outcomes of consolidation SCT.

6.4 Definitions

Response and progression will be evaluated using 2007 Revised Response Criteria for Malignant Lymphoma (modified). Please refer to definitions below and summarized in the table.

6.4.1 Complete Remission (CR)

The designation of CR requires the following (Table 5):

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.
2. A *post-treatment* residual mass of any size is permitted as long as it is PET negative. *If a pretreatment PET scan was negative*, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

6.4.2 Partial Response (PR)

The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by $\geq$50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement, will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. If the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. If the pretreatment PET scan was negative, CT criteria should be used.

6.4.3 Stable Disease (SD)

Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below).
2. The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. If the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

6.4.4 Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

1. Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.
2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with

no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
5. Lesions should be PET positive if disease lesions were PET positive before therapy, unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

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

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

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The level of risk attributed to this study requires High Intensity Monitoring as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which 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 an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is life-threatening.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly/birth defect.**
- **Is an important medical event.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- is unexpected (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied
- is related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience,

or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places human subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has actually occurred.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the study table. Routine AEs will be reviewed by the Data Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event (croqualityassurance@northwestern.edu). Completion of the NU CTO SAE Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:
- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)
- Country of incidence

All SAEs will be reported to, and reviewed by, the DSMC per the DSMP.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to Northwestern University and to the NU IRB within 5 working days of notification.
- Information pertaining to an NU subject that fits into any of the categories listed on the Reportable New Information page will be reported to the NU IRB within 5 business days of knowledge or notification.

7.3.3.3 Reporting to the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 Reporting to Takeda Pharmaceuticals

Regardless of expectedness or causality, all SAEs must also be reported to Takeda Pharmacovigilance or designee:

- **Fatal and Life Threatening SAEs** within 24 hours but no later than 4 calendar days from observation or awareness of the event
- **All other serious (non-fatal/non-life threatening) events** within 4 calendar days of observation or awareness of the event

The NU CTO SAE report form will be completed and submitted for all SAEs requiring reporting to Takeda Pharmacovigilance. Reports will include event term(s), serious criteria, intensity of the event(s), and causality of the event(s). Follow-up information on the SAE may be requested by Takeda.

The NU PI is responsible to ensure that the SAE reports are sent to Takeda Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the NU CTO QAM (as outlined above). NU must also provide Takeda Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s) as soon as possible but no later than 4 calendar days of such communication.

The contact for reporting is:
Takeda Pharmacovigilance or Designee
SAE and Pregnancy Reporting Contact Information
FAX Number 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator and NU CTO QAM immediately and permanently discontinue study drug. The QAM must fax a completed Pregnancy Form to the Takeda Department of Pharmacovigilance or designee. 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 QAM must also immediately fax a completed Pregnancy Form to the Takeda Department of Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

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 Takeda Quality representative.

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

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 Takeda Pharmacovigilance.

8.0 DRUG INFORMATION

8.1 Ixazomib

8.1.1 Other names

MLN9708

8.1.2 Classification - type of agent

Ixazomib is an orally bioavailable, potent, reversible, specific inhibitor of the 20S proteasome that has demonstrated antitumor activity in in vivo models of multiple myeloma (MM) [19]

8.1.3 Mode of action

Ixazomib has demonstrated antitumor activity in in vivo models of multiple myeloma (MM).

8.1.4 Storage and stability

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 at a temperature under 30ºC. Do not freeze. Ensure that the drug is used before the retest expiry date provided by Takeda. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

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, along with a medication diary for tracking all

doses. 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 at a temperature under 30ºC for the duration of each cycle. Medication should not be frozen. 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.

8.1.5 Protocol Dose & Administration

During induction treatment, ixazomib will be given orally twice per cycle (1 cycle = 21 days); the first dose will be on day 1 and the second on either day 8 or 15). The starting dose for phase I will be 2.3 mg. During maintenance treatment, ixazomib 4 mg will be given days 1, 8, and 15 of each cycle (1 cycle = 28 days during maintenance).

8.1.6 Preparation

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

8.1.7 Incompatibilities

None known.

8.1.8 Availability & Supply

Ixazomib will be supplied by Takeda Pharmaceuticals in strengths of 4.0, 3.0, and 2.3 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

To order drug, the Clinical Trial Material Form (see separate attachment) must be completed and faxed to Takeda (1-866-422-4797) for approval. Questions may be directed to Jim McNamara at 617-444-1619 or james.mcnamara@takeda.com.

NOTE:

- Orders are shipped Monday – Wednesday.
- Orders requests must be provided at least once week in advance of when drug is needed at the site.
- Emergency orders may be accommodated on a case by case basis.

8.1.9 Side effects

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment.

8.1.10 Return and Retention of Study Drug

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

8.2 Doxorubicin HCL

Please refer to the FDA-approved package insert for doxorubicin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.2.1 Other Names

Adriamycin PFSTM, Adriamycin RFSTM, Rubex®, hydroxydaunorubicin, hydroxydaunomycin, ADR

8.2.2 Classification – type of agent

Anthracycline antibiotic.

8.2.3 Mode of Action

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

8.2.4 Storage & Stability

Intact vials of doxorubicin solution should be stored in the refrigerator. Intact vials of powder for reconstitution should be stored at room temperature. Reconstituted solutions are stable for 7 days at room temperature and 15 days under refrigeration when protected from light. Commercially available solutions labeled as such are intended to be multidose vials. Compatibility and stability studies were conducted by the Pharmaceutical Development Service [60], Pharmacy Department, NIH Clinical Center, simulating concentrations of each drug that would be applicable to this trial. Admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, in polyolefin-lined IV bags were stable for up to 72 hours at room temperature, provided that the concentration of etoposide was < 250 mcg/ml.

8.2.5 Protocol Dose & Administration

Doxorubicin will be administered as a 96-hour continuous IV infusion, along with vincristine and etoposide in the same infusion solution. The chemotherapy will be administered with a suitable infusion pump via a central venous access device.

8.2.6 Preparation

Reconstitute the vials of doxorubicin powder with 5, 10, 25, or 50 mL, respectively, of sodium chloride for injection, USP, resulting in a concentration of 2 mg/mL. Doxorubicin will be admixed in 0.9% sodium chloride, along with vincristine IV for infusion over 24, 48 or 72 hours. Etoposide may be mixed with doxorubicin and vincristine, or it may be infused separately. See reference 49 for specific compatibility and stability information base on concentration of each agent.

8.2.7 Incompatibilities

Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

8.2.8 Availability & Supply

Doxorubicin is commercially available as a lyophilized powder for reconstitution in 10, 20, 50, and 100 mg vials. Also available are 2 mg/mL solutions for injection in 10, 20, 50, and 200 mg vials.

8.2.9 Side Effects

Hematologic: Leukopenia (dose-limiting), thrombocytopenia, anemia. Nadir in 10-14 days with recovery usually in 21 days.

Dermatologic: alopecia (usually complete; reversible) radiation recall reactions; increased sensitivity to sunlight.
Gastrointestinal: nausea and vomiting (doxorubicin is generally considered moderately to highly emetogenic), anorexia, diarrhea, mucositis (stomatitis, esophagitis).
Cardiovascular: cardiomyopathy may occur and is related to total cumulative lifetime dose. The risk for cardiomyopathy increases with total doses > 450 mg/m2. ECG changes and less often, arrhythmias, are seen. Rarely, sudden death has occurred.
Other: Red discoloration of urine for 24-48 hours after drug administration. Doxorubicin is a vesicant and can cause tissue necrosis if extravasated, especially at the concentration usually employed for bolus injections (i.e., 2 mg/mL).

8.3 Etoposide

Please refer to the FDA-approved package insert for etoposide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.3.1 Other Names

VePesid®, Epidophyllotoxin, VP-16, EPEG, NSC# 141540

8.3.2 Classification – type of agent

Podophyllotoxin derivative

8.3.3 Mode of Action

Etoposide inhibits the enzyme topoisomerase II, nucleoside transport, and incorporation, and causes DNA breakage

8.3.4 Storage & Stability

Intact vials of etoposide for injection should be stored at room temperature and protected from light. Compatibility and stability studies were conducted by the Pharmaceutical Development Service [60], Pharmacy Department, NIH Clinical Center, simulating concentrations of each drug that would be applicable to this trial. Admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, in polyolefin-lined IV bags were stable for up to 72 hours at room temperature, provided that the concentration of etoposide was < 250 mcg/ml.

8.3.5 Protocol Dose & Administration

Etoposide will be administered as a 96- hour continuous IV infusion, along with vincristine and doxorubicin. The chemotherapy will be administered with a suitable infusion pump via a central venous access device.

8.3.6 Preparation

Etoposide will be admixed in 0.9% sodium chloride for IV infusion over 24, 48 or 72 hours. Etoposide may be mixed with doxorubicin and vincristine or it may be infused separately. See reference 49 for specific compatibility and stability information based on concentration of each agent. Infusion solutions should be changed every 24 hours. The volume of the infusion solution will be determined by the 24 hour etoposide dose. If etoposide ≤ 150 mg per 24 hours, then dilute drugs in 500 mL 0.9% sodium chloride; if etoposide > 150 mg per 24 hours, then dilute drugs in 1000 mL 0.9% sodium chloride.

8.3.7 Incompatibilities

None known.

8.3.8 Availability & Supply

Etoposide is commercially available as a solution for injection in 5 mL, 7.5 mL, 25 mL, and 50 mL vials containing 20 mg/mL.

8.3.9 Side Effects

Myelosuppression, predominantly neutropenia and thrombocytopenia, is the most common toxicity associated with etoposide. Nausea and vomiting range from mild to severe in severity, depending on the dose. At the dose used in this study, etoposide is moderately highly emetogenic. Mucositis is also more common at the dose used in this study. Alopecia is likely. Hypotension is associated with too rapid administration of etoposide. This would be unlikely to occur in this trial.

8.4 Vincristine sulfate

Please refer to the FDA-approved package insert for vincristine sulfate for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.4.1 Other Names

VCR, Leurocristine sulfate, Oncovin®, Vincasar PFS, LCR

8.4.2 Classification – type of agent

Vinca alkaloid (tubulin inhibitor).

8.4.3 Mode of Action

Vincristine binds to tubulin, a protein that forms microtubules, thus interfering with spindle formation during metaphase and causing cessation of cellular mitosis.

8.4.4 Storage & Stability

Unopened vials should be stored under refrigeration and protected from light. Commercially available solutions labeled as such are intended to be multidose vials. Compatibility and stability studies were conducted by the Pharmaceutical Development Service [49], Pharmacy Department, NIH Clinical Center, simulating concentrations of each drug that would be applicable to this trial. Admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, in polyolefin-lined IV bags were stable for up to 72 hours at room temperature, provided that the concentration of etoposide was < 250 mcg/ml.

8.4.5 Protocol Dose & Administration

Vincristine will be administered as a 96-hour continuous IV infusion, along with etoposide and doxorubicin (see “Storage & Stability” above). The chemotherapy will then be administered with a suitable infusion pump via a central venous access device.

8.4.6 Preparation

Vincristine will be admixed in 0.9% sodium chloride for IV infusion over 24, 48 or 72 hours. Etoposide may be mixed with doxorubicin and vincristine or it may be infused separately. See reference 49 for specific compatibility and stability information based on concentration of each agent. Infusion solutions should be changed every 24 hours. The volume of the infusion solution will be determined by the 24 hour etoposide dose. If etoposide ≤ 150 mg per 24 hours, then dilute drugs in 500 mL 0.9% sodium chloride; if etoposide > 150 mg per 24 hours, then dilute drugs in 1000 mL 0.9% sodium chloride. Infusion solutions should be protected from light.

8.4.7 Incompatibilities
Furosemide; some in-line filters; polysiloxan containers used in portable delivery services.

8.4.8 Availability & Supply
Vincristine is commercially available in 1 mL, 2 mL, and 5 mL vials in a concentration of 1 mg/mL.

8.4.9 Side Effects
The most common toxicity associated with vincristine is neurotoxicity. Peripheral manifestations of neurotoxicity include: numbness of extremities, paresthesias, loss of deep tendon reflexes, neuropathic pain and muscle weakness. GI manifestations of neurotoxicity include constipation, and adynamic ileus. Cranial nerve manifestations include: diplopia, hoarseness, tinnitus, jaw pain (the latter usually occurring with the first dose of vincristine). Orthostatic hypotension & SIADH may also be seen. Vincristine is a vesicant and may cause tissue necrosis upon extravasation. This is more likely with bolus injections as opposed to dilute infusions

8.5 Cyclophosphamide
Please refer to the FDA-approved package insert for cyclophosphamide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.5.1 Other Names
Cytoxan®; Neosar®, CTX, CPM

8.5.2 Classification – type of agent
Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system.

8.5.3 Mode of Action
Cyclophosphamide metabolites are thought to disrupt cell division primarily by crosslinking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific.

8.5.4 Storage & Stability
Intact vials should be stored at room temperature. Reconstituted and diluted solutions are stable for 24 hours at room temperature and 6 days if refrigerated.

8.5.5 Protocol Dose & Administration
The total dose of cyclophosphamide will be administered by IV.

All patients should receive hydration with normal saline per institutional guidelines.

8.5.6 Preparation
Reconstitute 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials with 5, 10, 25, 50, or 100 mL of sterile water for injection or normal saline to give a final concentration of 20 mg/mL. Vigorous shaking and/or gentle warming may be necessary for non– lyophilized preparations. Bacteriostatic water for injection (paraben preserved only) may be used; benzyl alcohol derivatives may NOT be used.

8.5.7 Incompatibilities

Cyclophosphamide undergoes metabolic activation via cytochrome P450 3A4 in the liver and may potentially interact with any drug affecting the same isoenzyme. Inhibitors of 3A4 (e.g., itraconazole) could theoretically inhibit activation and inducers of 3A4 (e.g., phenytoin) could theoretically enhance activation of cyclophosphamide to active alkylating species. For the most part, such interactions have not yet been documented clinically.

8.5.8 Availability & Supply

Commercially available as a powder for reconstitution in 100 mg, 200 mg, 500 mg, 1 gram, and 2 gram vials.

8.5.9 Side Effects

Myelosuppression, hemorrhagic cystitis (patients must be well-hydrated before, during, and after treatment and have adequate renal function). Syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, alopecia, anorexia, nausea, vomiting, hyperuricemia, azoospermia, amenorrhea, cardiotoxicity (myocardial necrosis) usually at doses higher than those used in this study

8.6 Prednisone

Please refer to the FDA-approved package insert for prednisone for product information and a comprehensive list of adverse events.

8.6.1 Other Names

Deltasone, Orasone, Medicorten, Panasol-S, Liquid-Pred

8.6.2 Classification – type of agent

Adrenal corticosteroid

8.6.3 Mode of Action

Prednisone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, and minimal mineralocorticoid activity, and antineoplastic properties. As an antineoplastic agent, prednisone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

8.6.4 Storage & Stability

Store tablets, solutions and syrup in tightly closed containers at room temperature.

8.6.5 Protocol Dose & Administration

Oral.

8.6.6 Preparation

Not applicable.

8.6.7 Incompatibilities

None known.

8.6.8 Availability & Supply

Commercially available in 1, 2.5, 5, 10, 20, 25, and 50 mg tablets, or as an oral solution or syrup - 5 mg/5 ml (in 5% alcohol); solution concentrate - 5 mg/ml (with 30% alcohol).

8.6.9 Side Effects

Side effects likely to be encountered with intermittent high doses include: GI (dyspepsia, ulceration), insomnia, and hyperglycemia. Occasionally a “withdrawal syndrome” after short-term high doses, such as in this study, manifest muscle aches and pains. Immunosuppression with risk of infection is also seen.

8.7 Rituximab

Please refer to the FDA-approved package insert for rituximab for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.7.1 Other Names

Rituxan, IDEC-C2B8, chimeric anti-CD20 monoclonal antibody

8.7.2 Classification – type of agent

Antibody.

8.7.3 Mode of Action

Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. It binds with high affinity to CD20-positive cells, performs human effector functions in vitro, and depletes B cells in vivo. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis in vitro. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

8.7.4 Storage & Stability

Intact vials should be stored under refrigeration. Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

8.7.5 Protocol Dose & Administration

Rituximab will be administered as an IV infusion at 375 mg/m^2 on day 1 of each cycle of DA-EPOCH-R, immediately prior to the start of chemotherapy. Oral pre-medication 650 mg of acetaminophen and 50-100 mg diphenhydramine hydrochloride will be administered 30 to 60 minutes prior to starting each infusion of rituximab. The first rituximab infusion should be started at 50 mg/hr, and increased in 50-mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. If this rate of escalation is well tolerated the second and subsequent infusions can begin at a rate of 100 mg/hr and increase in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

8.7.6 Preparation

The desired dose of rituximab should be diluted in 0.9% NaCl or DW to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

8.7.7 Incompatibilities

Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

8.7.8 Availability & Supply

Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL.

8.7.9 Side Effects

The most severe serious adverse events associated with rituximab include severe infusion reactions, tumor lysis syndrome, and severe mucocutaneous reactions. Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab.

Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells (≥ 25,000/μL). Severe mucocutaneous reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills, and dyspnea. The mechanism of rituximab infusion reactions is thought to be secondary to release of cytokines. If a reaction occurs, then the infusion should be stopped until the symptoms resolve, and then restarted at a 50% slower rate.

Recent reports describe hepatitis B reactivation with fulminant hepatitis, hepatic failure and death in some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately 1 month after the last dose. Exacerbation or reactivation of other viral infections has also been reported with rituximab. Recent reports describe JC virus reactivation leading to progressive multifocal leukoencephalopathy (PML) in patients who were receiving rituximab. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for PML.

8.8 Filgrastim

Please refer to the FDA-approved package insert for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.8.1 Other Names

G-CSF; r-met HuG-CSF; Granulocyte Colony Stimulating Factor; Neupogen®

8.8.2 Classification – type of agent

Recombinant granulocyte-colony stimulating factor

8.8.3 Mode of Action

Filgrastim is a protein produced by E. Coli into which has been inserted the human G-CSF gene. Filgrastim differs from the natural protein in that the N-terminal amino acid is a methionine and it is not 0-glycosylated. G-CSF functions as a hematopoietic growth factor; it increases the proliferation, differentiation, maturation and release of precursor cells into mature blood cells of the neutrophil lineage. G-CSF has demonstrated in vitro effects on mature neutrophils, including an increase expression of chemotactic receptors, enhanced phagocytosis and intracellular killing of certain organisms, as well as enhanced killing of target cells that are bound by antibodies.

8.8.4 Storage & Stability
Intact vials and prefilled syringes should be stored in the refrigerator at 2-8° Centigrade (36-46° Fahrenheit). Do not freeze.

8.8.5 Protocol Dose & Administration
Filgrastim will be administered as a subcutaneous injection. In both arms, the daily dose will be 480 mcg.

8.8.6 Preparation
The desired dose of rituximab should be diluted in 0.9% NaCl or DW to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

8.8.7 Incompatibilities
Do not dilute with saline at any time; product may precipitate.

8.8.8 Availability & Supply
Commercial filgrastim is available in 1 mL and 1.6 mL vials containing 300 mcg and 480 mcg filgrastim, and in prefilled syringes containing 300 mcg/0.5 mL or 480mcg/0.8 mL.

8.8.9 Side Effects
The most common side effect associated with filgrastim is medullary bone pain. Bone pain is usually reported as mild or moderate and, if necessary, may be treated with non-opioid or opioid analgesics.

8.9 Pegfilgrastim
Please refer to the FDA-approved package insert for product information, and a comprehensive list of adverse events.

8.9.1 Other Names
Neulasta®

8.9.2 Classification – type of agent
Pegfilgrastim is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol.

8.9.3 Mode of Action
Similar to filgrastim.

8.9.4 Storage & Stability
Intact syringes should be stored under refrigeration and protected from light. Pegfilgrastim syringes are reportedly stable at room temperature for up to 48 hours prior to injection, if protected from light. Syringes that are frozen unintentionally may be allowed to thaw in the refrigerator. Pegfilgrastim syringes that have been frozen a second time should be discarded.

8.9.5 Protocol Dose & Administration
The dosage of pegfilgrastim is a single subcutaneous injection of 6 mg administered within 72 hours after completing the cycle. Pegfilgrastim will be administered as a subcutaneous injection.

8.9.6 Preparation
Not applicable.

8.9.7 Incompatibilities
Similar to filgrastim.

8.9.8 Availability & Supply
Pegfilgrastim is commercially available prefilled single-dose syringes containing 6 mg/0.6 mL of pegfilgrastim (10 mg/mL).

8.9.9 Side Effects
The most common side effect associated with pegfilgrastim is bone pain. Bone pain is usually reported as mild or moderate, and, if necessary, may be treated with non- opioid or opioid analgesics.

Other reported side effects include reversible elevations in LDH, alkaline phosphatase, and uric acid. These laboratory abnormalities are not usually of clinical significance and do not require any intervention

8.10 Methotrexate
Please refer to the FDA-approved package insert for product information and a comprehensive list of adverse events.

8.10.1 Other Names
MTX, amethopterin

8.10.2 Classification – type of agent
Methotrexate is a folate antimetabolite.

8.10.3 Mode of Action
Methotrexate competitively inhibits dihydrofolate reductase (DHFR); the affinity of methotrexate for DHFR is about one thousand-fold that of folate. DHFR catalyzes the conversion of dihydrofolate to the active tetrahydrofolate. Folic acid is needed for the de novo synthesis of the nucleoside thymidine, required for DNA synthesis. Also, folate is essential for purine and pyrimidine base biosynthesis, so synthesis will be inhibited. Methotrexate, therefore, inhibits the synthesis of DNA, RNA, thymidylates, and proteins.

8.10.4 Storage & Stability
Unopened vials of methotrexate should be stored at room temperature, and protected from light.

8.10.5 Protocol Dose & Administration
In this study, methotrexate will be administered as an intrathecal injection of 12 mg.

8.10.6 Preparation
For intrathecal injection: reconstitute to a concentration of 1-5 mg/mL with an appropriate sterile, preservative free medium such as Sodium Chloride Injection, USP.

8.10.7 Incompatibilities
The use of NSAIDs, probenecid, salicylates, or sulfonamides may prolong methotrexate levels and enhance toxicity.

8.10.8 Availability & Supply
Methotrexate is commercially available in 2 mL (25 mg/mL) vials or 20 mg, 25, mg, 50 mg, or 100 mg vials for reconstitution. Read the manufacturer’s package labeling carefully for solution concentrations.

8.10.9 Side Effects

Toxicities associated with intrathecal administration: arachnoiditis, ataxia, coma, confusion, dementia, encephalopathy, headache, paresis, seizures

9.0 SPECIMEN BANKING

During the phase II portion of the study, patients may agree to have one red top tube and one green top tube drawn on day 1 of induction Cycles 1 & 2 (pre-dose), and day 1 of the first 3 maintenance cycles. These samples will be drawn at the time of standard of care draws. Blood will be frozen and stored in the Biorepository of the Pathology Core Facility at Northwestern University for future, unspecified use. Frozen samples from all sites will be shipped in batches to the Biorepository at the following address:

ATTN: Jeremy Mathews
Pathology Core Facility
Northwestern University
Robert H. Lurie Comprehensive Cancer Center
710 N. Fairbanks Ct
Olson Pavilion Room 8419
Chicago, IL 60611
Office (312)503-3753
Pager (312)695-8675
email:jmathews@northwestern.edu

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

Phase I dosing will consist of dose finding with ATD, as specified in previous sections. Phase II will then commence based on the RP2D identified by Phase I.

10.2 Sample Size and Accrual

Approximately 3-9 patients are anticipated for Phase I, and 46 patients for Phase II. Patients from the first Phase who are treated at the MTD/RP2D and who are evaluable for response endpoints will be included in the Phase II efficacy analysis and will count towards total enrollment for Phase II. The phase I sample size is based on clinical consideration. As such, we expect to enroll a minimum of 5 patients, and a maximum of 9, in Phase I, and do not plan additional formal statistical analysis of these patients.

With respect to efficacy, our null hypothesis is that DA-EPOCH-R plus ixazomib will yield no difference in one-year PFS as compared to that observed in DHL, a rate we estimate at 40% based upon historical controls 1. We believe that the combination of DA-EPOCH-R plus ixazomib will warrant further validation if we can demonstrate improvement in one-year PFS by approximately 20%, to a rate of 60%. The Phase II sample size is determined based on Simon's two stage design using PFS as the binary endpoint. We propose an Optimal Two-Stage Design to test the null hypothesis that P</=0.40 versus the alternative that P>=0.60, where P represents one-year PFS. We propose error probability limits of $\alpha>0.05$ and $\beta<0.20$. The Optimal Two-Stage Design provides for early stoppage of the trial if there is sufficient indication of futility 2. Under these conditions, if seven or fewer of the first 16 patients are alive and progression-free at one year, the trial will be terminated, and DA-EPOCH-R plus ixazomib considered as having no greater efficacy than previously-reported treatment regimens. However, if eight or more patients are alive and progression-free, the trial will proceed, to a total enrollment of 46 patients. If the number responding at this point is less than or equal to 23, the combination will not be considered superior to previously-reported regimens. Enrollment/treatment on this trial will NOT be stopped for sake of interim analysis; if there is evidence of futility once a sufficient number of patients have reached one year, any others enrolled before that time may continue per protocol.

Should the study unexpectedly close early due to reasons other than efficacy (e.g. loss of funding/continued support from Takeda, or other unforeseen reasons that are outside of

the PI's control), sample size and statistical plan may be amended at that time, if deemed appropriate by the biostatistician and PI.

10.3 Data Analyses Plans

Data will be summarized for baseline, for phase 1, for phase 2, and for safety analyses. Most of these analyses will be descriptive and estimative in nature. PFS and OS will be estimated by Kaplan-Meier methods, which will account for loss to follow up.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

Amendments to the protocol will be initiated and maintained by the assigned Medical Writer. Requests for revisions may come from multiple sources, including but not limited to the Principal Investigator, study team, drug company, or FDA. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Janssen Scientific Affairs. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Trials Office (CTO) at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CTO website for additional instructions on registering a patient.

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.
- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the Institutional Review Board (IRB). Protocol deviations must be reported according to the policies and procedures of the IRB of record.

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has compromised the rights and welfare of the research subject
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

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APPENDIX I – PROTOCOL HISTORY OF CHANGES

Amendment 1 (Version 2.0) – July 13, 2015			
Section(s) Affected	***Initial***	***2.0 Version***	***Rationale***
Sections 2.1.1 (Primary Objectives/Phase I) , 4.4.1 (Dose Limiting Toxicities) and 6.1 (Primary endpoints)	N/A	DLT definitions modified to include Grade 5 cytopenias	FDA review panel suggestion
Amendment 2 (Version 3.0) – Nov 30, 2015			
Section(s) Affected	***2.0 Version***	***3.0 Version***	***Rationale***
Face Page	N/A	IND number added	Administrative
Face Page, Patient Eligibility (Sec 3.0)	Listed Adam Petrich as PI and IND holder and Mitul Gandhi as Sub-Investigator	Lists Barbara Pro as PI and IND holder, removes Mitul Gandhi as Sub-Investigator, and adds Jason Kaplan as Sub-Investigator	Administrative due to transition in faculty
Signature Page	Includes signature page	Removes signature page	Administrative
Schema	Listed prednisone dosing as daily	Lists prednisone dosing as BID (twice daily)	Clarification
Schema	"SCT"	"Stem Cell Transplant (SCT)"	Clarification
List of Abbreviations	n/a	Additional abbreviations included (CNS, IT, LP)	Clarification
Inclusion criteria (Sec 3.1.3, 3.1.7and 3.1.10)	• Sec 3.1.3 – Criteria listed only Myc-rearrangement • Platelets and bone marrow involvement listed in one note • Sec 3.1.10 - negative pregnancy test within # days	• Sec 3.1.3 – Criteria broadened to include Myc-rearrangement/amplification/over-expression • Sec 3.1.7 – Bone marrow involvement listed first for emphasis and only applies to ANC and platelet exceptions • Sec 3.1.10 - negative pregnancy test within 28 days	• To allow participation for subjects with the expanded criteria. • Revised for clarity • Information on the # of days was inadvertently missed
Exclusion criteria (Sec 3.2.1 and 3.2.7)	• Patient can have 1 cycle of prior chemotherapy • The note for this exclusion criteria only referred to prior exposure to HBV without describing the assay method	• Prior chemotherapy should have a washout period of 3 weeks, and steroids are permitted • Clarified the note to include prior exposure to both HBV & HCV and the assay to be used for detection.	• Clarification on prior treatment • To improve clarity
Ixazomib (Sec 4.3.1.)	n/a	Adds language that dosing will occur after labs in the hospital or clinic during induction and day 1 of maintenance. Also adds that patients should have weekly labs assessed during cycles 7 and 8.	Improved clarity for dosing instructions

DA-EPOCH-R (Sec 4.3.2)	n/a	• Adds "inpatient" to administration summary • Adds stipulation for Rituximab spanning longer than one day	• Clarification • Allows flexibility in DA-EPOCH-R administration, which is standard of care
DA-EPOCH-R (Sec 4.3.2), CNS Prophylaxis and Treatment (Sec 4.7)	n/a	Adds clarifications on LP requirements and "per institutional standards"	Allows flexibility in DA-EPOCH-R administration,
Maintenance Therapy Dose Modifications for Ixazomib (Sec 4.5.2)	Table: "Ixazomib Dose Adjustments"	Table: "Ixazomib Dose Adjustments *During Maintenance*"	Clarification to distinguish Induction from Maintenance
Concomitant Medications (Sec 4.6.1)	Listed Lamivudine or Tenofovir as antiviral treatments.	To add Entecavir as an alternative to Lamuvidine/Tenofovir for treatment of Heb B/C in the case subjects may test positive for past exposure to the virus during baseline screening but may be not be clinically active.	Per discussions with PI
Permitted Concomitant Medications/Procedures (Sec 4.6.3)	n/a	Lists steroids used to control lymphoma as permitted medication	Per discussions with PI
Supportive Care (Sec 4.8)	n/a	Adds Antibiotic Prophylaxis (Sec 4.8.7) as permitted/recommended supportive care	Per discussions with PI
Replacement of Subjects (Sec 4.11)	Subjects who complete less than 1 cycle will be replaced.	"Subjects who receive at least 1 dose of investigational treatment are evaluable for toxicity. However, should a patient come off treatment within the DLT period for any reason other than a DLT (e.g. patient refusal, unrelated adverse event) an additional patient may be added to the cohort at the discretion of the QAM and DSMC."	Clarification requested by QAM
Study Procedures (Sec 5.0)	Column for "After C2 of Induction AND between Induction & Maintenance"	Column separated into three: "Induction (C1-6): Day 1" "Induction (C1-6): Day 8/15" "Maintenance(C7+): Day 1 (+/- 1 day)	Revised for clarity
	Footnote 2: PET/CT required until maintenance	PET/CT only required at baseline and after cycle 2 induction. Thereafter, PET/CT or CT alone both acceptable. Also clarifies timing with windows	Allows investigator discretion and clarity
	Footnote 3: Pregnancy test within 28 days	Footnote 3: Pregnancy test within 7 days	Aligns more closely with standard requirements
	MYC and BCL2 by FISH and IHC listed as 4 separate rows	MYC and BCL2 by FISH and IHC combined into a single row with details in footnotes 5 and 6	Combined for simplification
	Footnote 6: "With the exception of	Footnote 6: "IHC is preferred but not required for enrollment"	Clarification to specifically

	MYC by FISH, tests can be done before or after enrollment"		address IHC
	Footnote 7: n/a	Footnote 7: Adds language about maintenance treatment dosing, timing, and windows	Added for clarity
	Footnote 10: All labs were required within 14 days	Footnote 10: FISH and IHC have no window for registration	FISH and IHC are not time-sensitive
	n/a	Footnote 11: Adds specific language for HBV and HCV requirements	Added for clarity
	n/a	Adds row for "Lumbar Puncture" and Footnote 12 for details	Added for clarity
	n/a	Adds row for "DA-EPOCH-R Administration" and Footnote 13 for details	Added for clarity
	n/a	Adds row for "Ixazomib Administration" and Footnote 14 for details	Added for clarity
	"Off Treatment" column does not include timing	Adds Footnote 15 to say that visit should occur 21 days (+/- 7 days) from last study treatment	Added for clarity
	n/a	Adds Footnote 16 to say that labs must be checked weekly at Cycle 7 and Cycle 8 prior to ixazomib dosing	Added for clarity
Specimen Banking (Sec 9.0)	Temperature conditions for shipment was not clear	Specified that samples for specimen banking from affiliate sites must be shipped frozen.	To improve clarity

Amendment 3 (Version 4.0) – Mar 3, 2016			
Section(s) Affected	***3.0 Version***	***4.0 Version***	***Rationale***
Cover page, Eligibility (Sec 3.0)	Listed "Tufts University School of Medicine"	Changes to "Tufts Medical Center"	Administrative correction
Schema, DA-EPOCH-R Administration (Sec 4.3.2), Induction Therapy Dose Modifications (Sec 4.5.1), Study Table (Sec 5.0 #13)	All chemo agents for DA-EPOCH-R were to be given inpatient with Rituximab on Day 1	Allows for Rituximab to be given in an outpatient setting per institutional standard of care 1 to 3 days prior to day 1 or after EPOCH during Cycle 1	Institutional standard of care does not always allow for inpatient Rituximab. Added language allows flexibility for affiliate sites
List of Abbreviations	n/a	Additional abbreviations included (DHL, GCB)	Clarification
Eligibility (Sec 3.0)	Included template instructions inadvertently	Removes template instructions	Clarification
Inclusion Criteria (Sec 3.1.1)	Included an incomplete statement: "B-cell lymphoma, unclassifiable, with features intermediate	Removes comparative language to rea simply: "B-cell lymphoma, unclassifiable"	Clarification; PI believes initial language was a mistake

	between DLBCL"		
Exclusion Criteria (Sec 3.2.1)	Allowed for patients to have one cycle of NHL chemotherapy prior to starting study treatment	Also allows patients who have had no prior chemotherapy	Per PI discussion; simplifies treatment plan, assessment schedule and study objectives
Induction Therapy Dose Modifications (Sec 4.5.1)	• n/a • Listed Ixazomib dose as "TBD" in table of dose levels	• Patients do not need to come off study for dose delays during induction • Changes dose level to "MTD"	• Allows flexibility since the study treatment is expected to cause cytopenia • Clarification – the dose will be determined during the study
Study Procedures (Sec 5.0)	• #1: n/a • #2: n/a • #4: Listed TMA at screening • #5: MYC+ must be confirmed by FISH	• #1: Includes a 7-day window for physical exam and ECOG status at C1D1 • #2: Encourages diagnostic CT but it is not required • #4: Moves TMA to C1D1 • #5: MYC+ can be confirmed by FISH and IHC	• PI feels a 7 day window is appropriate & allows flexibility • Clarification • QA request – TMA isn't needed for registration • Clarification to be consistent with Inclusion 3.1.3
Schema, DA-EPOCH-R (Sec 4.3.2)	Rituximab allowed to be given outpatient if necessary	Clarifies that rituximab can be given outpatient at select institutions.	The intent of allowing outpatient rituximab was for the inclusion of an external site. For consistency, sites should not switch internally between outpatient and inpatient administration.
Study Procedures (Sec 5.0)	#10,11: All labs were to be assessed within 14 days of registration, including Hep B and C	#10,11: Hepatitis B and C can now be assessed within 28 days of registration	PI feels that Hepatitis testing can have a longer window
Pharmacokinetics and Drug Metabolism (Sec 1.2.2)	Outdated data about ixazomib metabolism and its interactions with CYP isozymes	Contains updated metabolism data taken directly from Takeda's newest protocol template.	To align with updated drug data from sponsor
Exclusion Criteria (Sec 3.2.6), Prohibited Concomitant Medications (Sec 4.6.2), Permitted Concomitant Medications (Sec 4.6.3)	Excluded the use of strong inhibitors of CYP1A2, strong inhibitors of CYP3A, and strong CYP3A	Now only excludes CYP3A inducers CYP1A2 and CYP3A inhibitors are not excluded	Updated metabolism data for ixazomib suggest that concomitant treatment with such inhibitors is

	inducers		acceptable
Amendment 4 (Version 5.0) – December 14th, 2016			
Section(s) Affected	***4.0 Version***	***5.0 Version***	***Rationale***
Cover Page; Study Summary; 3.0 (Patient Eligibility)	n/a	Adds Reem Karmali as Northwestern sub-investigator and Deepa Jagadeesh as sub-investigator at Cleveland Clinic	Administrative – added faculty and affiliate site
Cover Page; 1.3 (Rationale for the Current Study); 4.6.3 (Permitted Concomitant Medications / Procedures); 7.3.3.4 (Reporting to Takeda Pharmaceuticals); 8.1.4 (Storage and Stability); 8.1.8 (Availability & Supply)	Lists funding source as Millennium Pharmaceuticals	Changes funding source to Takeda Pharmaceuticals	Administrative – funding source changed name
Schema; 4.3.2 (DA-EPOCH-R); 4.5.1 (Induction Chemotherapy Dose Modifications); 4.7 (CNS Prophylaxis and Treatment)	Patients to receive IT methotrexate with each cycle if diagnostic LP is negative	Adds that IT methotrexate will be given per physician's discretion using institutional guidelines	Clarification – standard of care procedures may mean that methotrexate is not given with every cycle for these patients
Schema; Study Summary; 4.1 (Overview); 4.2.2 (Maintenance)	Patients may receive maintenance ixazomib for up to one year "or as long as deriving benefit"	Changes language to say: "if a patient is receiving clinical benefit after this period, an extension of ixazomib can be considered with documented approval from Takeda, the study PI and NU DSMC"	Clarification – a discussion will need to take place for any possible extension of ixazomib
Study Summary	Listed short title of protocol as "DA-EPOCH-R plus Ixazomib in MYC-aberrant NHL	Removes short title	Administrative – short title not required; removed to avoid discrepancies
2.1.1 (Phase I Primary Objective); 4.4.1 (Dose Limiting Toxicities)	CTCAE v4.0	References CTCAE v4.03	Administrative update
3.1.3 (Inclusion Criteria)	Specifies that FISH for MYC-rearrangement does not require central review	Removes language "does not require central review"	Not relevant
4.1 (Overview); 4.4 (Dose Escalation Schema – Phase I Induction Only)	n/a	Adds the following statement to reflect the completion of the phase I portion of the study: "The MTD was established at cohort 2. As of August 10, 2016, all	The Phase I portion is now complete and MTD established at 3mg ixazomib

		patients will be treated with ixazomib at 3mg during induction."	
4.3.2 (DA-EPOCH-R)	Chemotherapy to be given inpatient	Removes "inpatient" reference and replaces with "per institutional guidelines"	To allow for varied methods of administration at affiliate sites
4.3.2 (DA-EPOCH-R); 4.4 (Dose Escalation Schema – Phase I Induction Only); 4.5 (Dose Modifications); 5.0 (Study Procedures)	n/a	Adds consecutive table numbers to all existing tables	Clarification for easier referencing
4.4.1 (Dose Limiting Toxicities)	DLT is defined as any Grade 3 toxicity during cycle 1	Adds that DLT is defined as any Grade 3 drug-related toxicity during cycle 1	Clarification
4.5.1 (Induction Chemotherapy Dose Modifications)	Listed specific instructions and dose levels for DA-EPOCH-R dose adjustments to be strictly followed.	States that doses may be delayed as clinically warranted up to 3 weeks, and that dose modifications will take place as appropriate per institutional guidelines. Adds specific exceptions (as footnotes) to dose adjustment guidelines for vincristine, prednisone, and methotrexate.	Standard of care DA-EPOCH-R administration includes specific exceptions for dose modifications of prednisone and vincristine, specifically for older patients and neuropathy for vincristine.
4.5.2 (Dose Modifications for Ixazomib [Induction and Maintenance])	Dose modifications were listed for ixazomib during maintenance only	Now includes instructions for ixazomib dose delays and modifications during both induction and maintenance. Dose delays can take place during either induction or maintenance. Dose modifications can only take place during maintenance, and this has been clarified with two separate sections.	Clarification; the PI feels that it is clinically appropriate to delay ixazomib during induction as well as maintenance but keep the dose level consistent while its given with chemotherapy
4.6.1 (Required Concomitant Medications/Procedures)	• Listed Bactrim DS as 1 table three times weekly • HepB/C sAg+ patients should receive lamivudine, entecavir, or tenofovir	• Lists Bactrim DS given "with dosing per institutional guidelines" • HepB/C sAg+ patients should receive those medications listed *or* equivalent per institutional guidelines	To allow for varying regimens at affiliate sites
5.0 (Study Procedures)	• n/a • n/a • #1: Respirations were required as part of vital	• Adds windows of ±3 days to each study visit • Adds a footnote (#4) to clarify timing of CBC	• Clarification to avoid deviations • Clarification • Respirations not

	signs • #2: PET/CT required at "time of diagnosis" • Listed TMA as a requirement • #10: Labs to be completed within 14 days of registration, 28 days for other procedures. Includes longer window for patients who completed prior chemo • #11: HBV and HCV testing was required within 28 days of registration	and Chemistry labs • Removes "respirations" from vital signs • #2: PET/CT required at baseline • Removes TMA requirement • #10: All screening procedures to be completed within 28 days with exception of labs. Remove longer window. • #11: HBV and HCV testing is now required ≤42 days (6 weeks) prior to registration	clinically necessary • #2: Clarification; time of diagnosis is likely earlier than the 28 days prior to registration • TMA was not being performed and is not needed • #10: Overall window is more inclusive of all procedures. Patients are not allowed to have prior chemo. • #11: The window has been extended as the PI feels is clinically appropriate
5.0 (Study Procedures, #8); 9.0 (Specimen Banking)	Study labs were to be drawn at baseline, only for Phase II patients	Study labs should be drawn on day 1 of induction cycles 1 & 2, rather than baseline, and only for Phase II patients **who agree to optional blood draws**	An additional time point was added for study labs, and all samples were made optional to accommodate affiliates
Amendment 5 – December 5th, 2017 *Approved by Scientific Review Committee: December 4, 2017*			
Section(s) Affected	***Amd 5 Version***	***Amd 5 Version***	***Rationale***
Cover Page	Included Jason Kaplan as sub-I	Removes Jason Kaplan and adds Valerie Nelson as sub-I	Administrative faculty updates; Jason Kaplan has left the institution, and Lake Forest will be utilized for patient care on this study.
Cover Page, Study Summary, 3.0 (Patient Eligibility)	n/a	Adds Medical College of Wisconsin as an affiliate site	Administrative
Heading	n/a	Adds NU and Takeda study numbers for reference	Administrative
4.3.2 (DA-EPOCH-R)	n/a	Adds statement: "*Dosing schedule and administration for prednisone may vary if appropriate per institutional standards or physician discretion."	Per standard of care, variance in dosing should be permitted.
Amendment 6 – May 22, 2018 *Approved by Scientific Review Committee: May 26, 2018*			
Section(s) Affected	***Amd 5 Version***	***Amd 6 Version***	***Rationale***
Cover Page; Study Summary; 3.0 (Patient Eligibility)	PI at Tufts University was listed as Andrew Evens	Updates Tufts PI to Andreas Klein and adds Rutgers University as sub-site with Andrew	Administrative change; Andrew Evens is now affiliated with Rutgers and is still participating

		Evens as PI	in the study. Andreas Klein has taken over at Tufts.
3.1.8 (Inclusion Criteria)	n/a	Adds clarification of HIV allowance. Patients with HIV are eligible for the study if they meet specific criteria	Clarification from Takeda
8.1.4 (Storage & Stability – Ixazomib)	Ixazomib was to be stored at 2ºC to 8ºC (36ºF to 46ºF)	Ixazomib should now be stored under 30ºC and not frozen	To align with updated storage information for new supply of ixazomib issued by Takeda
8.5.5 (Protocol Dose & Administration)	Referred to a table for specific saline dosing for hydration	Removes reference to specific dosing and states that saline should be given "per institutional guidelines"	There was no table to be referenced, and PI feels that institutional practice is acceptable
Amendment 7 – May 8, 2019 *Approved by Scientific Review Committee: May 20, 2019*			
Section(s) Affected	***Amendment 6 Version***	***Amendment 7 Version***	***Rationale***
Cover Page	Listed Alfred Rademaker as the biostatistician	Replaces Alfred Rademaker with Borko Jovanovic as the new biostatistician	Administrative research staffing change
Cover Page and Throughout	The Coordinating Center was referred to as the Clinical Research Office (CRO)	The Coordinating Center is referred to as its new name, the Clinical **Trials** Office (CTO)	Administrative update to account for a change in the Coordinating Center's name; the Coordinating Center itself remains the same
List of Abbreviations and Throughout	Committee name listed as "Data Monitoring Committee"	Committee name updated to "Data **and Safety** Monitoring Committee"	Administrative update to account for a change in the Committee's name; the Committee itself remains the same
Inclusion Criterion 3.1.1	N/A	Adds a note to clarify that histology must be CD20-positive to be eligible	Clarification due to the mechanism of action of rituximab to target CD20.
Inclusion Criterion 3.1.9	Stated: Females of childbearing potential must use contraception through **90 days** after the last dose of study drug	States: Females of childbearing potential must use contraception through **12 months** after the last dose of study drug	Updated to align with new safety recommendations for rituximab
Sections 4.1, 4.2, and 4.5.2.1 (Treatment Plan); Table 5-1 footnote 14 (Study Procedures)	N/A	Added note stating: If a patient has dose reduced the ixazomib during the treatment phase (when it was given in combination with chemotherapy) and	Clarification that aligns with what had already been stated in Sections 1.3, 4.1, and 5.0.

		now enters the maintenance phase (where ixazomib will be administered as a single agent), they should start maintenance at the full dose of ixazomib (rechallenge at 4 mg weekly), not at the reduced dose.	
Table 4-3, Footnote e	Stated: Dose delays are permitted for any length necessary	Sates: If ixazomib is interrupted for > 3 weeks, DSMC approval must be obtained in order for patients to resume treatment per Section 4.5.2.1.	Corrected discrepancy to match Section 4.5.2.1
Section 6 (Endpoints)	Stated: Patients must complete at least 2 cycles of induction therapy to be evaluable for response endpoints.	States: Patients must complete at least 2 cycles of induction therapy **and undergo a subsequent disease response assessment** to be evaluable for response endpoints.	Clarification requested by the PI
Section 10.2 (Sample Size and Accrual)	N/A	States: Should the study unexpectedly close early due to reasons other than efficacy (e.g. loss of funding/continued support from Takeda, or other unforeseen reasons that are outside of the PI's control), sample size and statistical plan may be amended at that time, if deemed appropriate by the biostatistician and PI.	Insertion of standard language to account for future circumstances that may merit a change to the statistical plan
Throughout	N/A	Corrects minor grammatical and formatting changes	Administrative update
Amendment 8 – January 16, 2020			
Section(s) Affected	***Amendment 7 Version***	***Amendment 8 Version***	***Rationale***
Title Page and Throughout	Protocol version dated May 8, 2019 (Amendment 7)	Updated to protocol version dated January 16, 2020 (Amendment 8)	Administrative update
Table of Contents	N/A	Updates page numbers	Administrative update
Study Summary; Section 10.2 (Sample Size and Accrual)	N/A	Adds the following text: Patients from the first Phase who are treated at the MTD/RP2D and who are evaluable for response endpoints will	Clarification. Updates the statistical analysis plan to specify which subjects will be included in the sample population for the Phase II efficacy

		be included in the Phase II efficacy analysis and will count towards total enrollment for Phase II.	analysis.
Section 7.2.4 (UPIRSO); Section 7.3.3.2 (Reporting to the NU IRB) Section 7.3.3 (Expedited Reporting of SAEs/Other Events); Section 11.2 (Amendments); Section 11.6.2 (Other Protocol Deviations); Section 11.8 (Publication Policy)	N/A	Updates standard language to align with new Northwestern University protocol template	Administrative update
Throughout	n/a	Minor corrections to typographical errors, style, and formatting.	Administrative update.