Phase I/II Study of Ixazomib and Romidepsin in Relapsed/ Refractory Peripheral T-cell Lymphoma (PTCL)

Sponsor Investigator
Ryan A. Wilcox, MD, PhD
University of Michigan Rogel Cancer Center

Statistician
Philip S. Boonstra, Ph.D.

Trial Management
Big Ten CRC Administrative Headquarters at Hoosier Cancer Research Network, Inc.
500 N. Meridian, Suite 100
Indianapolis, IN 46204

Trial Support
Takeda Pharmaceutical Company
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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

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Site Investigator Name (printed)

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SYNOPSIS

TITLE	Phase I/II Study of Ixazomib and Romidepsin in Relapsed/ Refractory Peripheral T-cell Lymphoma (PTCL)
PHASE	I/II
OBJECTIVES	Primary Objective: Phase I: To evaluate the safety of ixazomib when given in combination with romidepsin to establish the maximum tolerated dose (MTD) of this combination. Phase II: To determine the complete response (CR) rate of this combination in relapsed/refractory PTCL. Secondary Objectives: 1. To determine the overall response rate (ORR) 2. To determine the duration of response (DOR) 3. To determine the time to next treatment (TTNT) 4. To determine the overall survival (OS) Correlative/Exploratory Objectives: 1. To examine TNFR2 and HR23B expression as predictive biomarkers 2. To biobank diagnostic biopsy specimens and other biologic specimens (i.e., blood, serum, plasma) for future correlative studies.
STUDY DESIGN	Open label, single arm, non-randomized trial
KEY ELIGIBILITY CRITERIA	**Inclusion criteria (see section 3.1):** 1) Ability to voluntarily provide written IRB-approved informed consent and communicate satisfactorily with the investigator, to participate fully in the study, and comply with all its requirements. 2) Age ≥ 18 years at the time of consent. 3) Histological confirmation of peripheral T-cell lymphoma (PTCL). 4) Documented disease progression after receiving at least one prior therapeutic regimen. 5) Prior cancer treatment must be completed at least 21 days prior to C1D1 or 5 times the half-life of the drug(s), whichever is greater . Systemic steroids at a dose less than the equivalent of 10 mg/day of prednisone and inhaled, nasal, and topical steroids are permitted. Intermittent dexamethasone for the treatment of nausea/emesis is also permitted if it is not greater than 40 mg/month. 6) Adequate hematological function: a. ANC ≥1,000 cells/uL b. Platelets ≥75,000 cells/uL 7) Adequate hepatic function: a. Bilirubin ≤1.5 times the specific institutional upper limit of normal (ULN) b. AST and ALT each ≤3 x ULN (or ≤5.0 x ULN in the presence of

	known hepatic involvement) 8) Adequate renal function: a. Calculated creatinine clearance ≥30 cc/min using Cockcroft-Gault. **Exclusion Criteria (see section 3.2):** 1) A history of, or a concurrent, clinically significant illness, medical condition or laboratory abnormality that, in the investigator's opinion, could affect the conduct of the study. 2) Pregnant or lactating female: all females of child-bearing potential must have a negative serum pregnancy test within 14 days of Day 1. 3) CNS lymphoma 4) Major surgery or radiation therapy within 28 days of study registration 5) Uncontrolled infectious disease, including active herpes simplex or herpes zoster 6) Known positive test for Hepatitis B surface antigen, Hepatitis C, or HIV 7) Difficulty swallowing or malabsorption 8) ECOG performance status >2 9) Prior treatment with bortezomib, ixazomib, or romidepsin. 10) Has received any prior systemic therapy within 21 days of treatment or within 5 times the half-life of the drug(s). 11) Peripheral neuropathy (≥grade 2) 12) No other malignancy within 2 years, except nonmelanoma skin cancers or carcinoma in situ.
STATISTICAL CONSIDERATIONS	**Phase I:** We will estimate the MTD among one of three dose levels of romidepsin plus a fixed dose of ixazomib. Dose assignments will be made according to the TITE-CRM design, with each patient assigned to a dose level as he/she is enrolled (based on the available DLT information at the time). We will target a rate of DLT of 0.25 and enroll patients until either (i) 18 have been treated at one dose, and the next enrolled patient would also be assigned to that dose level or (ii) a total of 36 patients have been enrolled across all dose levels combined. The estimated MTD is the dose level with a model-estimated rate of DLT closest to 25% (but not more than 33%) after 36 patients have been enrolled (or the dose level where 18 patients have been treated, and the next enrolled patient would also be assigned to that dose level). The (up-to) 18 patients at the estimated MTD will comprise the interim analysis of a 2-stage phase II study of efficacy of this dual-agent therapy. The patients will be evaluated for CR and comprise an interim futility analysis for the dual-agent therapy. If at least 3 of the (up-to) 18 patients show CR, we will proceed to the second stage of the phase II. **Phase II:** Upon successful completion of the phase 1 design/interim efficacy analysis, we will transition to a final evaluation of the efficacy of the dual-agent ixazomib and romidepsin at the MTD. We will test the null hypothesis that the rate of CR is 15%. Additional patients will be enrolled to the dual-agent MTD estimated from the phase I step, for a total of up to 30 patients at the MTD (up to 18 from Phase 1 + 12 from Phase II). When all patients have been followed for response status, if at least 8 patients

	demonstrate CR, we will declare the dual-agent MTD to be sufficiently efficacious. With 30 patients, this is an empiric CR rate of 27%. If the true CR rate is 0.15, this will occur with probability 0.068 (type I error); if the true CR rate is 0.35, this will occur with probability 0.87 (power).
TOTAL NUMBER OF SUBJECTS	N = 18-36 (phase I) + 12 (phase II) total evaluable patients will be required. Patients who withdraw their consent during either stage of the study prior to the first response assessment will be replaced.
ESTIMATED ENROLLMENT PERIOD	24 months
ESTIMATED STUDY DURATION	36 months

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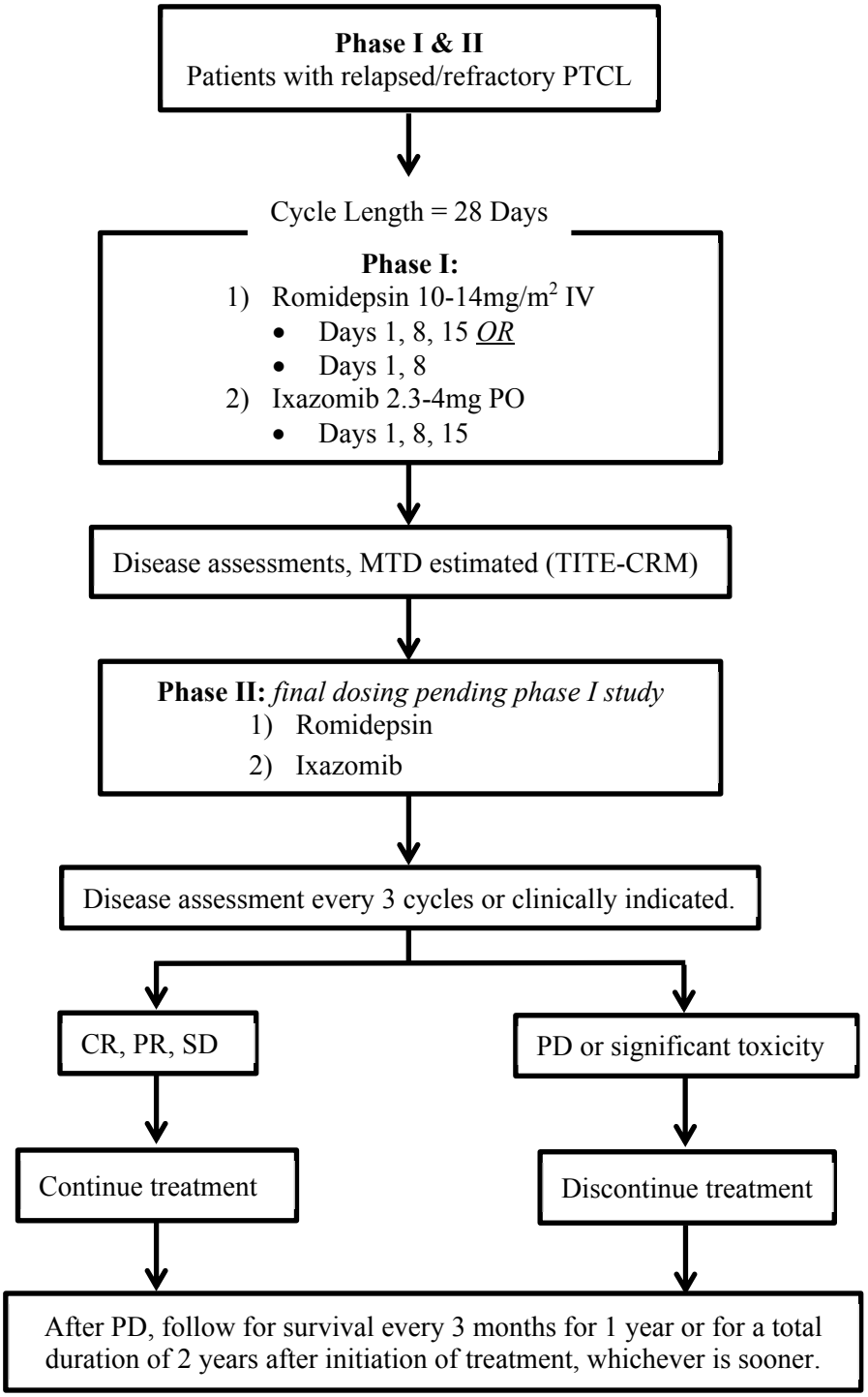
SCHEMA



MTD= Maximum tolerated dose; TITE-CRM= Time-to-Event Continual Reassessment Method

1. BACKGROUND AND RATIONALE

1.1 Peripheral T-cell Lymphoma Background

Approximately 10-15% of non-Hodgkin lymphomas (NHL) are derived from mature (i.e. post-thymic) T lymphocytes [1]. The heterogeneity of these lymphomas and poor understanding of their pathogenesis continue to impede their classification and the development of novel therapeutic strategies. This is highlighted by the sobering observation that the most common subtype of peripheral T-cell lymphoma (PTCL) lacks any distinguishing characteristics and is designated by the World Health Organization as "PTCL, unspecified (PTCL-U)" [1,2]. While the development of combination immunochemotherapy (e.g. "R-CHOP") has led to significant survival benefits in B-cell NHL, the PTCLs are associated with inferior responses to therapy and overall survival [3]. In fact, the vast majority of PTCL patients will ultimately succumb to their disease, most within a few years of diagnosis [1,2,4]. Novel therapeutic strategies are needed if improved outcomes are to be achieved. The observation that PTCL incidence rates are increasing faster than almost any other subgroup of NHL further heightens this sense of urgency [5,6].

Anthracycline-based therapies (e.g. CHOP) remain the mainstay of therapy for PTCL, even though the survival benefit associated with this approach remains uncertain[2,7]. More intensive induction regimens and consolidation with high-dose chemotherapy followed by autologous stem-cell transplantation are frequently employed strategies, but primary refractory disease and early relapses are common. Three novel agents, belinostat, pralatrexate and romidepsin, were granted FDA approval for relapsed/refractory PTCL and are associated with overall response rates of approximately 26% [8], 29%[9] and 25-38%[10,11], respectively. A complete response rate of ≈11% is observed in patients treated with belinostat or pralatrexate as single agents. However, longer follow up in patients treated with the HDAC inhibitor romidepsin demonstrates that complete remissions achieved with this agent may be durable, thus raising the question as to whether this agent may have curative potential in a subset of "exceptional responders" [12]. The arsenal of treatment continues to grow with time; however, the overall response rates for PTCLs are not satisfactory and further developments for better disease control are necessary.

Brentuximab vedotin also received FDA approved for the treatment of relapsed/refractory anaplastic large cell lymphoma (ALCL), a subtype of PTCL, based on phase II, open-label study of 58 patients. The overall response rate in this study was 86% with a complete response rate of 57% with a median duration of 13.2 months [13]. Grade 3/4 adverse events occurred in >10% of patients and included neutropenia, thrombocytopenia, and peripheral sensory neuropathy[13]. Another phase II, open-label, multicenter study evaluated the response rate of Brentuximab vedotin in relapsed CD30+ non-hodgkin lymphomas which included PTCL and angioimmunoblastic T-cell lymphoma (AITL). The overall response rate in these cases was 41% with a complete response rate of 24% [14]. The duration of response is quite variable and short with the reported median duration of response of 7.6 months; however, the median duration of a complete response had not been reached at the time of the initial analysis[14]. Grade 3/4 events were similar to that of the ALCL study with neutropenia, peripheral sensory neuropathy and hyperkalemia being the most common events [14]. Brentuximab is a promising treatment agent but the most significant limitation is the need for continued treatment which is limited by cytopenias and peripheral neuropathy. Despite the use of these novel agents, the outlook for PTCL patients with relapsed/refractory disease remains grim, and novel therapeutic strategies are needed.

1.2 Standard of Care - Romidepsin

Romidepsin was granted FDA approval for relapsed/refractory PTCL and is associated with an overall response rate of 25-38%[10,11]. Patients treated with the approved HDAC inhibitors romidepsin and belinostat may anticipate CR rates of 15% and 10.8%, respectively [8]. Among patients achieving a CR/CRu with romidepsin (n=19), 53% were durable (≥12 months) [12]. It is given intravenously on a weekly schedule and associated with grade 3/4 adverse events in 18-30% of patients. See section 10.0 for drug information.

1.3 Investigational Treatment – Ixazomib (NINLARO, MLN9708)

Ixazomib is a small molecular proteasome inhibitor that was approved for use in November 2015 in multiple myeloma when administered in combination with other therapies. Multiple trials have investigated ixazomib in various malignancies including multiple myeloma, AL amyloidosis, lymphoma, and nonhematologic cancers.

Preclinical Experience:
For the most current pre-clinical information on Ixazamib, please refer to the Investigator's Brochure (IB).

Mechanism of Action
Ixazomib is a reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.

Ixazomib induced apoptosis of multiple myeloma cell lines in vitro. Ixazomib demonstrated in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. In vivo, ixazomib demonstrated antitumor activity in a mouse multiple myeloma tumor xenograft model.

PK & Safety
Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to first maximum plasma concentration (Tmax) of approximately 0.5 to 2.0 hours and terminal t1/2 after multiple dosing of approximately 5 to 7 days (10). Results of a population PK analysis (N = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA (11). Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. See the IB for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708

treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

Summarize relevant clinical studies –
Patients have been treated with different doses of MLN9708, either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in the current ixazomib Investigator's Brochure.

Safety info
The emerging safety profile indicates that oral MLN9708 is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care. Additionally, the AEs in the combination studies are consistent with the safety profile of the individual agents in the combination regimen (eg, myelosuppression is common in regimens containing melphalan, and rash is common in regimens containing lenalidomide). There was no evidence of cumulative or long-term toxicity in the ixazomib+LenDex regimen with a median follow-up of almost 2 years as of the July 2015 data cutoff. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention.

The most common SAEs were pneumonia (244 patients) and pyrexia (83 patients) in clinical studies using oral ixazomib. In the overall safety population in studies with oral ixazomib, 625 patients reported at least 1 drug in the study regimen that resulted in study drug discontinuation. The most common AEs that resulted in discontinuation of at least one of the drugs were peripheral neuropathies (45 patients), asthenic conditions (44 patients), thrombocytopenia (33 patients), pneumonia (26 patients), diarrhea (26 patients), acute kidney injury (19 patients), neutropenia (14 patients), septic shock (14 patients), general physical health deterioration (13 patients), maculopapular rash (13 patients), insomnia (13 patients), anemia (12 patients), and plasma cell myeloma (10 patients).

Clinical investigation of the potential benefit of ixazomib is ongoing through a comprehensive and global development plan that involves several studies sponsored by Millennium. Across the program, ixazomib appears to show signs of antitumor 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 multiple myeloma (NDMM), and prolongs stabilization of the underlying disease in other patients across all ongoing studies.

Although additional data are needed to characterize the clinical benefit of this drug across additional indications, the emerging data support the continued development of ixazomib for the treatment of patients with hematologic and solid tumor malignancies.

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agentMLN9708 is administered weekly in patients with RRMM or RRAL, respectively.

Rationale for starting dose
The starting dose of 4mg was established as this is the FDA approved starting dose for ixazomib when in combination with other agents. This dosage demonstrated an acceptable safety profile when in combination with lenalidomide and dexamethasone.

Absorption
After oral administration, the median time to achieve peak ixazomib plasma concentrations was one hour. The mean absolute oral bioavailability was 58%, based on population PK analysis. Ixazomib AUC increases in a dose proportional manner over a dose range of 0.2 to 10.6 mg.

A food effect study conducted in patients with a single 4 mg dose of ixazomib showed that a high-fat meal decreased ixazomib AUC by 28% and Cmax by 69%. Therefore, ixazomib should be taken at least 1 hour before or at least 2 hours after food.

Distribution
Ixazomib is 99% bound to plasma proteins and the extent of binding is not altered by severe renal impairment, moderate hepatic impairment, or severe hepatic impairment. Ixazomib distributes into red blood cells with a blood-to-plasma AUC ratio of 10. The steady-state volume of distribution is 543 L.

Elimination
The renal clearance of ixazomib was approximately 0.119 L/hr which is 6.4% of the total clearance, thereby indicating that renal clearance does not meaningfully contribute to ixazomib clearance in humans. The terminal half-life (t1/2) of ixazomib was 9.5 days and the mean plasma clearance was 1.86 L/hr based on the population PK analysis.

Metabolism
Metabolism by multiple CYP enzymes and non-CYP proteins is expected to be the major clearance mechanism for ixazomib. At clinically relevant ixazomib concentrations, in vitro studies using human cDNA-expressed cytochrome P450 isozymes showed that no specific CYP isozyme predominantly contributes to ixazomib metabolism. At higher than clinical concentrations, ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6%), 2D6 (5%), 2C19 (5%) and 2C9 (< 1%).

Excretion
After administration of a single oral dose of ^{14}C-ixazomib to 5 patients with advanced cancer, 62% of the administered radioactivity was excreted in urine and 22% in the feces. Unchanged ixazomib accounted for < 3.5% of the administered dose recovered in urine, suggesting that most of the total radioactivity in urine was attributable to metabolites.

Potential Drug interactions
Avoid concomitant administration of Ixazomib with strong CYP3A inducers. See section 5.3.2 for further information.

See section 10.1 for additional drug information and refer to the current Ixazomib Investigator's Brochure (IB).

1.4 Rationale

NF-κB is constitutively activated and promotes the growth and survival of malignant cells in T-cell lymphoproliferative disorders[15-26]. Furthermore, constitutive NF-κB activation is an adverse prognostic factor in PTCL, as NF-κB positive cases are associated with a 2-year overall survival of 42%, compared with a 2-year overall survival of 68% in NF-κB negative cases [27]. Inhibition of NF-κB signaling represents one mechanism of the proteasome inhibitor bortezomib in T-cell lymphomas[28]. Proteasome inhibition undoubtedly targets other proteins and signaling pathways in PTCL, but these are not well defined [29-31]. While the mechanisms of resistance (and susceptibility) to proteasomal inhibition are poorly understood, recent studies in cutaneous T-cell lymphomas (CTCL) demonstrate that tumor necrosis factor receptor 2 (TNFR2) is overexpressed in approximately 20% of CTCL, where it drives non-canonical activation of NF-κB and thus confers resistance to proteasomal inhibition[32]. While TNFR2 expression has not been formally examined in a large PTCL cohort, increased plasma levels of its soluble form (sTNFR2) are associated with poor survival in PTCL[33]. In contrast, mutations rendering NF-kB resistant to IkB-mediated cytoplasmic sequestration likely confer resistance to proteasomal inhibition[32]. Not surprisingly then, bortezomib has promising *in vitro* and *in vivo* activity in T-cell lymphoproliferative disorders[22,24,31,34,35]. In a small phase II study, an overall response rate of 67% (17% complete remissions) was observed in fifteen CTCL/PTCL-U patients. As anticipated, treatment was well tolerated, and all responses lasted 7-14+ months[35]. Our preliminary experience with ixazomib in relapsed/refractory PTCL demonstrates evidence of activity and to date, seven PTCL patients have been treated and the complete response rate was 14% with one PTCL patient achieving a CR for 1 year. Knowing that NF-kB activation promotes T-cell lymphomagenesis and confers resistance to chemotherapy in malignant T cells [19,36-38] we evaluated other mechanisms of resistance.

We have recently identified a molecularly and clinically distinct subset of PTCL, NOS that highly expresses the zinc-finger transcription factor GATA-3 [[39,40], please see associated commentary[41]; further reviewed in[42]]. In our cohort, no long-term disease-free survivors were appreciated among patients with GATA-3$^+$ PTCL, NOS [39], and similarly poor outcomes have been independently observed [43,44]. The dismal outcomes associated with GATA-3$^+$ PTCL, NOS may be attributed, at least in part, to the high rate (>50%) of chemotherapy resistant (primary refractory) disease observed in these patients [38]. More recently, we have demonstrated in both loss-of-function and gain-of-function studies that GATA-3 directly promotes chemotherapy resistance in a cell-autonomous manner in malignant T cells [38].

GATA-3 has cell-autonomous and non-cell autonomous functions, including the regulation of chemotherapy resistance, in T-cell lymphomas. We sought to examine the potential role of GATA-3 in mediating chemotherapy resistance in T-cell lymphomas (TCL). Therefore, cell growth and viability were examined using TCL cell lines stably transduced with non-targeting or GATA-3-targeting shRNA, as previously published[39]. Given their molecular heterogeneity, including loss of p53, these particular cell lines were selected for scrutiny[16,19,22,36,45-47]. GATA-3 loss was associated with a significant decrease in chemotherapy resistance, both *in vitro* and *in vivo* [38]. Interestingly, following chemotherapy administration and complete regression of tumors in mice injected with H9 cells expressing GATA-3-targeting shRNA, tumors recurred following cessation of chemotherapy administration. GATA-3 expression was examined by immunohistochemistry in these recurrent tumors. As previously published,

GATA-3 knockdown is observed in tumor xenografts obtained from untreated mice[39], but the tumors that reemerge following chemotherapy administration highly express GATA-3. Using a previously described cohort of patients[39], GATA-3 expression was examined in paired biopsies obtained at diagnosis and at the time of relapse. An approximately two-fold increase in GATA-3 expression was observed following treatment. These findings suggest that chemotherapy imposes a positive selection pressure for TCL subclones that highly express GATA-3, and provides further evidence for its role in mediating resistance to chemotherapy. The relationship between GATA-3 expression and primary refractory disease following treatment with anthracycline-based multiagent chemotherapy was examined. Primary refractory disease was observed in 11.8% of GATA-3 negative PTCL, NOS (n=17), in contrast to 52.6% of GATA-3 positive PTCL, NOS (n=19). In addition to its cell-autonomous functions, GATA-3 dependent gene targets, particularly Th2-associated cytokines, likely contribute to its non-cell-autonomous functions via regulation of the tumor microenvironment. For example, we observed that antigen-presenting cells, particularly lymphoma-associated macrophages (LAM) are abundant constituents of the TME in most TCLs[39,48]. More importantly, *in vitro* studies demonstrated that LAM directly promote the growth and survival of malignant T cells[48,49], and that GATA-3 dependent cytokines regulate their functional polarization [39]. Therefore, GATA-3 may confer resistance to chemotherapy in both a cell-autonomous and non-cell-autonomous (and tumor microenvironment-dependent) manner.

HDAC inhibition abolishes GATA-3 DNA binding and impairs the expression of its gene targets. Post-translational acetylation (and deacetylation) regulates the function of many non-histone proteins, including transcription factors. For example, multiple members of the GATA family of transcription factors (e.g. GATA-1, 2, and 4) are acetylated by the "histone" acetyltransferase p300/CBP [50-52]. Seven lysine-rich regions are present in GATA-1, six of which are conserved in GATA-3. Mutation of one such region impairs GATA-3 dependent transcription[53]. Transcription factor acetylation may promote (or inhibit) DNA and/or co-factor binding that is required for transcriptional regulation [54]. The crystal structure of GATA-3's DNA binding domain in complex with its DNA target demonstrate that several conserved lysine residues are either intimately involved in DNA binding or are required for an intramolecular interaction required for GATA-3's tertiary structure [55]. Collectively, these observations suggest that the DNA binding capacity, and hence function, of GATA-3 may be regulated by its acetylation state. Importantly, "histone" deacetylase (HDAC) inhibition decreases Th2- (and GATA-3-) dependent cytokine (e.g. IL-4, IL-5, and IL-13) production by malignant T cells, while increasing the production of cytokines (i.e. Th1-associated cytokines, including interferon-γ) that are normally suppressed by GATA-3 [56]. Collectively, these observations suggest that HDAC inhibition may alter GATA-3's acetylation state and be associated with a loss in its ability to regulate gene transcription. To examine this possibility, we first sought to demonstrate, by chromosome immunoprecipitation (ChIP) studies, that GATA-3 binds its predicted gene targets in malignant T cells, particularly primary TCL specimens. We have demonstrated in a well characterized TCL cell line (i.e. H9 cells [39]) and in primary samples (including formalin-fixed, paraffin-embedded tissue), that GATA-3 binds the Th2-associated cytokine genes (IL-5 and IL-13) and the chemokine receptor CCR4. These gene targets were selected for examination as they are "classic" GATA-3 dependent gene targets in conventional T cells, and more importantly, their expression is highly enriched in the GATA-3$^+$ subset of PTCL, NOS [39,40]. Furthermore, we have confirmed in shRNA-mediated loss-of-function studies that these are bona fide GATA-3 target genes [39]. Having confirmed GATA-3 binding to these gene targets, we next examined the extent to which treatment with clinically available HDAC inhibitors (HDACi) alter GATA-3 DNA binding. We have observed that brief (e.g. 4 hour) exposure to clinically available HDAC inhibitors

(including vorinostat, romidepsin, and belinostat) abolishes GATA-3 DNA binding in both TCL cell lines and primary samples and the expression of its gene targets. We have not observed any alteration in total GATA-3 expression or nuclear localization following HDACi treatment. In coupled immunoprecipitation and immunoblotting studies, we have demonstrated that HDAC inhibition regulates the extent of GATA-3 acetylation (data not shown). These innovative findings suggest that HDAC inhibition disrupts GATA-3 DNA binding and target gene expression. If so, this finding would have significant clinical implications, suggesting that HDAC inhibitors may overcome chemotherapy resistance in GATA-3-expressing T-cell lymphomas.

GATA-3 expression is not only NF-kB dependent [38,57], but is also required for the homeostatic survival [57,58], differentiation [59], and migration [60] of conventional T-cell subsets. Consistent with its role in conventional T cells, we have previously shown that GATA-3 is an NF-κB target gene in malignant T cells and confers their resistance to chemotherapy in a cell-autonomous manner [38]. Not surprisingly, GATA-3 expression has both diagnostic and therapeutic implications [40], and its expression has successfully identified high-risk PTCL patients who are unlikely to achieve a remission with conventional chemotherapeutic agents [44]. Therefore, the observation that ixazomib led to significant inhibition of both NF-κB and GATA-3 in primary TCL specimens *ex vivo* and following one month of treatment in the single responder treated in this study is noteworthy. Consistent with our findings, Ravi et. al. observed that ixazomib induced apoptosis in multiple T-cell lymphoma cell lines and was associated with widespread changes in gene expression.

Proteasome inhibition is synergistic with other therapeutic strategies, including HDAC inhibition[61], and likely overcomes mechanisms of chemotherapy resistance in T-cell lymphomas[22,36]. While the median OS in rel/refr PTCL is <6 months[7,62,63], a subset of patients treated with romidepsin achieve a durable CR (>12 months), that is associated with prolonged OS[12].

Therefore, we propose a multi-center phase II study with ixazomib and romidepsin in patients with relapsed/refractory PTCL. Since this is a novel combination, the phase I endpoint is to determine the dose limiting toxicity and maximum tolerated dose and the phase II endpoint is to determine the CR rate of this combination.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Phase I: To evaluate the safety of ixazomib when given in combination with romidepsin to establish the maximum tolerated dose (MTD) of this combination.

Phase II: To determine the complete response (CR) rate of this combination in relapsed/refractory PTCL.

2.1.2 Secondary Objectives

1. To determine the overall response rate (ORR)
2. To determine the duration of response (DOR)
3. To determine the time to next treatment (TTNT)

4. To determine the overall survival (OS)

2.1.3 Correlative/Exploratory Objectives

1. To examine TNFR2 and HR23B expression as predictive biomarkers
2. To biobank diagnostic biopsy specimens and other biologic specimens (i.e., blood, serum, plasma) for future correlative studies.

2.2 Endpoints

2.2.1 Primary Endpoint

Phase I: Dose limiting toxicities (DLTs) based on adverse event (AE) evaluation defined by CTCAE v4.03 of the combination of ixazomib and romidepsin.

Phase II: CR, defined as complete metabolic response recorded from first day of treatment until disease progression or initiation of new antineoplastic therapy, as per the Lugano response criteria.

2.2.2 Secondary Endpoints

- OR, defined as complete or partial metabolic response recorded from first day of treatment until disease progression/recurrence or initiation of new antineoplastic therapy, as per the Lugano response criteria.
- DOR, defined as time that measurement criteria are met for complete or partial metabolic response (whichever status is recorded first) until disease progression/recurrence or initiation of new antineoplastic therapy, as per the Lugano response criteria.
- TTNT defined as the date of initiation of treatment until death or the date of initiation of the next treatment.
- OS, defined as time from first day of treatment to time of death.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0-2 within 14 days prior to registration.

4. Histological confirmation of peripheral T-cell lymphoma (PTCL) and biopsy confirmation of disease relapse (after initial or any subsequent salvage therapy within 6 months of enrollment).

5. Documented disease progression after receiving at least one prior therapeutic regimen.

6. Prior cancer treatment must be completed at least 21 days prior to C1D1 or 5 times the half-life of the drug(s), whichever is greater, and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to ≤ Grade 1 or baseline. Systemic steroids at a dose less than the equivalent of 10 mg/day of prednisone and inhaled, nasal, and topical steroids are permitted. Intermittent dexamethasone for the treatment of nausea/emesis is also permitted if it is not greater than 40 mg/month.

7. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)[1]	≥ 1000/mm^3
Platelets (Plt)[2]	≥ 75,000/mm^3
Renal	
Calculated creatinine clearance	≥ 30 cc/min using the Cockcroft-Gault formula
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN), (exception of Gilbert disease)
Aspartate aminotransferase (AST)	≤ 3 × ULN, if known hepatic involvement then ≤ 5 × ULN
Alanine aminotransferase (ALT)	≤ 3 × ULN, if known hepatic involvement then ≤ 5 × ULN
[1]ANC: GCS-F is not allowed to meet ANC criteria. Subjects with significant marrow involvement will be discussed on a case-by-case basis with the Sponsor Investigator. [2]Platelets: Platelet transfusion not allowed within 3 days of blood draw.	

8. Females of childbearing potential must have a negative serum pregnancy test within 14 days prior to registration. **NOTE:** Females are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months

9. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 90 days after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

10. Males must be willing to abstain from donating sperm or semen from the time of informed consent until 90 days after treatment discontinuation.

11. The subject must have the ability to understand and comply with study procedures for the entire length of the study, as determined by the treating physician or protocol designee.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. A history of, or a concurrent, clinically significant illness, medical condition or laboratory abnormality that, in the investigator's opinion, could affect the conduct of the study.

2. Active infection requiring systemic therapy

3. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

4. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, or other cancer for which the subject has been disease-free for at least two years.

5. Active central nervous system (CNS) lymphoma

6. Major surgery or radiation therapy within 28 days of study registration

7. Uncontrolled infectious disease, including active herpes simplex or herpes zoster

8. Known positive test for Hepatitis B surface antigen, Hepatitis C, or HIV. NOTE: testing is not required.

9. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of oral medications including difficulty swallowing, as determined by the treating physician.

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

11. Q-T interval, based on Bazett-corrected interval > 0.48 sec

12. Treatment with any investigational drug within 21 days prior to registration or within 5 times the half-life of the investigational drug.

13. Peripheral neuropathy ≥ grade 2

14. Prior treatment with bortezomib, ixazomib, or romidepsin.

15. Systemic treatment, within 14 days of Cycle 1 Day 1, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort. See section 5.5.2.

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

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

18. Prior autologous hematopoietic stem cell transplant within 60 days of study registration.

19. Prior allogeneic hematopoietic stem cell transplant.

4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten CRC Administrative Headquarters' electronic data capture (EDC) system. A subject is considered registered when an On Study date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within **5 business days** of registration.

5. TREATMENT PLAN

Single arm phase I/II study of ixazomib and romidepsin in relapsed/refractory PTCL.

5.1 Phase I Dose Escalation Study

The phase I study includes three dose levels. Each cycle is 28 days. Patients will continue to receive therapy until progressive disease, unacceptable toxicity, or if any other withdrawal criteria are met.

Dose level	Romidepsin	Ixazomib
4 (start)	10mg/m^2 IV on days 1, 8, 15	4 mg PO on days 1, 8, 15
5	14mg/m^2 IV on days 1, 8	4 mg PO on days 1, 8, 15
6	14mg/m^2 IV on days 1, 8, 15	4 mg PO on days 1, 8, 15

Dose assignments during phase 1 will be made according to the TITE-CRM design[82]. The first patient enrolled will be assigned to dose level 4. Subsequent patients will be assigned to a dose level based on the estimated probability of DLT (as determined by a statistical model; see Section 12.1 for details). Each patient will be assigned to a dose level as he/she is enrolled (based on the information available at the time). A new patient does not have to wait for previous patients to complete the first cycle before being assigned to a dose level. However, to ensure safety, no patient will be assigned to dose level 5 or 6 until at least one patient has completed the first cycle at dose level 4 with no DLTs.

Enrollment will continue until either (i) 18 patients have been treated at one dose level, and the next enrolled patient would also be assigned to that dose level, or (ii) a total of 36 patients have been enrolled across all dose levels combined.

The estimated MTD is the dose level with a model-estimated rate of DLT closest to 25% (but not more than 33%) after 36 patients have been enrolled (or the dose level where 18 patients have been treated, and the next enrolled patient would also be assigned to that dose level).

NOTE: After the first six patients have completed the first cycle, if the estimated rate of DLT at dose level 4 exceeds 0.33, the trial will stop for toxicity.

5.2 Phase II Study

The (up-to) 18 patients treated at the estimated MTD from phase I will comprise the interim analysis of a 2-stage phase II study of efficacy. If at least 3 of the (up-to) 18 patients have a CR, we will proceed to the second stage of the phase II (where 12 patients will be enrolled).

The phase II study will include treatment with ixazomib and romidepsin at the MTD established in the Phase I study. Each cycle is 28 days and patients will receive treatment until progressive disease, unacceptable toxicity, or if any other withdrawal criteria are met.

5.3 Pre-medication and Hydration

Pre-medications: dexamethasone 12mg PO/IV prior to romidepsin, as per institutional standards. Anti-retroviral prophylaxis with acyclovir or a similar medication is recommended to start with initiation of therapy following local guidelines.

5.4 Romidepsin + Ixazomib Administration

Drug	Dose[1]	Route	Schedule[2]	Cycle Length
Romidepsin	10-14mg/m^2	Intravenously (IV) as per institutional standard	Days 1, 8, 15 or Days 1, 8	28 days
Ixazomib	2.3-4 mg	PO after romidepsin[3]	Days 1, 8, 15	

[1] Body surface area (BSA) should be recalculated when weight changes by ≥ 10% according to local guidelines.
[2] A window of +/- 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).
[3] Ixazomib should be taken once a week on the same day (± 3 days as above) for the first three weeks of a four-week cycle. There should be at least 72 hours between doses. Ixazomib should be taken at least one hour before or at least two hours after food. The whole capsule should be swallowed with water. The capsule should not be crushed, chewed or opened. If vomiting occurs after taking a dose, the patient should not repeat the dose. The patient should resume dosing at the time of the next scheduled dose.

5.5 Concomitant Medications

5.5.1 Allowed Concomitant Medications

All treatments the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

The following medications and procedures are permitted during the study:

- Antiemetics, preferably non- 5-HT3 serotonin receptor antagonists may be used at the discretion of the investigator. The dose and regimen will be according to institutional

guidelines. If 5-HT3 serotonin receptor antagonists are required to nausea refractory to initial agents, then monitoring the QT interval is necessary with periodic EKGs.

- IV fluids should be given to prevent volume depletion.
- Potassium and magnesium supplements
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice. 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.
- 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.
- Warfarin or Coumarin derivatives are allowed; however, prolongation of the PT and elevation of INR has been observed in patients receiving concomitant romidepsin and warfarin.

Refer to section on Supportive Care to ensure it is reconciled with allowed concomitant medications.

5.5.2 Prohibited Concomitant Medications

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study.

- A DDI with a strong inhibitor would increase romidepsin exposure.
  - Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
  - Strong inhibitors of CYP3A or P-gp: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir.

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
  - Use of rifampin is not permitted as it *increases* the exposure to romidepsin and this is likely due to rifampin's inhibition of an undetermined hepatic uptake process that is predominantly responsible for the disposition of romidepsin. It is unknown if other potent CYP3A4 inducers alter the exposure of romidepsin.
- The dietary supplement St John's wort is not permitted.

The following procedures are prohibited during the study:

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

- Platelet transfusions to meet eligibility criteria are not allowed within 3 days before study drug dosing.
- Adjuvant hormone therapy for breast or prostate cancer.

Examples of inhibitors, inducers, and substrates can be found in Appendix III and at http://medicine.iupui.edu/clinpharm/ddis/table.aspx.[64]

5.6 Supportive Care

5.6.1 Romidepsin

Treatment with romidepsin has led to myelosuppression, infections, electocardiographic changes, and tumor lysis syndrome. Management regarding these events is outlined below and please refer to standard guidelines for management.

Myelosuppression

Treatment can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia. Monitor blood counts regularly during treatment with romidepsin, and modify the dose as described in Section 6.2.

Electrocardiographic Changes

Several treatment-emergent morphological changes in EKGs (including T-wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown. In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, consider cardiovascular monitoring of EKGs at baseline and periodically during treatment. Confirm that potassium and magnesium levels are within normal range before administration of romidepsin.

Tumor Lysis Syndrome

In patients with Stage III/IV disease and/or high tumor burden are at greater risk for tumor lysis syndrome and should be closely monitored, and managed as per standard guidelines.

Nausea and/or Vomiting

Antiemetics: prefer that non-5-HT3 serotonin receptor antagonists be used at the discretion of the investigator. The dose and regimen will be according to institutional guidelines. If 5-HT3 serotonin receptor antagonists are required for to nausea refractory to initial agents, then monitoring the QT interval is necessary with periodic EKGs.

Fluid deficits should be corrected before initiation of study drug and during treatment.

5.6.2 Ixazomib

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

Prophylaxis against Risk of Infection

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

as acyclovir or valacyclovir will be initiated as clinically indicated. Other antivirals are also acceptable, as clinically indicated.

Nausea and/or Vomiting

Antiemetics: prefer that non-5-HT3 serotonin receptor antagonists be used at the discretion of the investigator. The dose and regimen will be according to institutional guidelines. If 5-HT3 serotonin receptor antagonists are required for nausea refractory to initial agents, then monitoring the QT interval is necessary with periodic EKGs.

Fluid deficits should be corrected before initiation of study drug and during treatment.

Diarrhea

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

Erythematous Rash With or Without Pruritus

As with VELCADE, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents for which rash is an overlapping toxicity. The rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body 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 first incidence of rash events occurred early during treatment, and there was no evidence of increased frequency of rash with prolonged exposure. The rash is often transient, self-limiting (resolves without medical intervention), and is typically Grade 1 to 2 in severity.

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

In line with clinical practice, dermatology consult and biopsy of ≥Grade 3 rash or any SAE involving rash are recommended at the discretion of the investigator. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). The rare risks of Stevens-Johnson syndrome, TEN, DRESS syndrome, and pemphigus vulgaris have been reported in oncology studies when ixazomib (or placebo) has been given in a multi-therapy regimen, with concomitant medications known to cause rash, and/or in the setting of confounding TEAEs. These severe, potentially life-threatening, or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Study medications should be discontinued in the event of severe, potentially life-threatening rash.

Thrombocytopenia
Thrombocytopenia has been reported to date primarily at the higher doses tested. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Thrombocytopenia nadirs commonly recover without intervention by the beginning of the next scheduled cycle. Ixazomib administration should be modified as noted as per dose modification recommendations in Table 6.2 when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia
Neutropenia has been reported. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable with G-CSF according to standard clinical practice. Neutropenic nadirs commonly recover without intervention by the beginning of the next scheduled cycle or with a short delay in treatment. Ixazomib administration should be modified when neutropenia occurs, as noted in the dose modification recommendations in Table 6.2. Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

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

Hypotension
Symptomatic hypotension and orthostatic hypotension 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.

Posterior Reversible Encephalopathy Syndrome
Posterior reversible encephalopathy syndrome (PRES), which ultimately resolved, has been reported with ixazomib. PRES is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging. If the syndrome is diagnosed or suspected, symptom-directed and medical treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors. Prompt diagnosis and initiation of antihypertensive and anticonvulsant therapy are important to prevent irreversible end-organ damage.

Transverse Myelitis
Transverse myelitis has been reported with ixazomib. It is not known whether ixazomib causes transverse myelitis; however, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

Progressive multifocal leukoencephalopathy
PML, which may be fatal, has occurred in less than 1% of oncology patients receiving ixazomib in combination with other cancer therapies. It is not known whether ixazomib causes PML; however, the possibility that ixazomib may have contributed to PML cannot be excluded. In the event of occurrence of PML, ixazomib should be discontinued and supportive care provided as needed.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose limiting Toxicity (DLT) and Maximally Tolerated Dose (MTD)

Phase I: DLTs occurring during the 1st cycle of treatment with the combination of ixazomib and romidepsin will be used for dose-escalation decisions. The *true* MTD is defined as the largest dose at which no more than 25% of patients experience a DLT; the *estimated* MTD will be the dose level with a model-estimated rate of DLT closest to 25% (but not more than 33%).

Definition DLT: A DLT is defined as any of the following adverse events (AEs) that are possibly, probably, or definitely related to the combination of ixazomib and romidepsin that occurs during the 1st cycle (28 days). The NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4 will be used to assess toxicities.

Toxicity Category	Drug-Related Toxicity/Grade
Hematologic	Grade 4 Neutropenia for ≥ 14 days
	Febrile neutropenia: Grade 3 or 4 neutropenia with fever > 38ºC, both sustained over a 24-hour period
	Anemia, Grade 3 or 4
	Thrombocytopenia: Grade ≥ 4 lasting greater than 7 days or Grade ≥ 3 complicated by at least a Grade 2 hemorrhage
Non-Hematologic	Grade 3 or 4 toxicity (excluding alopecia, fatigue or anorexia lasting < 7 days, or Grade 3 nausea and/or vomiting that persists for < 2 days following appropriate supportive care). Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy

Toxicity Category	Drug-Related Toxicity/Grade
Infection	Grade 3 or Grade 4
Any	Grade 5
Electrolyte abnormalities	Grade ≥ 3 electrolyte abnormalities that do not resolve to ≤Grade 2 or baseline within 7 days
Grade 4 leukopenia or lymphopenia will NOT be considered a DLT	

6.2 Dose Modifications

Dose modifications below are outlined for the Phase I portion of the trial. Further information on the Phase II dose modification will be determined after the MTD is established.

Treatment with romidepsin and ixazomib will use a cycle length of 28 days. Missed doses within a cycle will not be made up. For example, if drug is held on Day 8 and given the next week, the day of administration will be Day 15; Day 8 will be considered as missed. Once a dose of romidepsin or ixazomib is reduced, the dose may only be re-escalated after discussion with and approval by the sponsor investigator. If a delay occurs on day 1 of a cycle, then day 1 will be when the first dose of a cycle is given.

For a new cycle of treatment to begin or resumption of treatment within a cycle, the patient must meet the following criteria:

- ANC ≥ 1,000/mm^3.
- Platelet count ≥ 75,000/mm^3.
- Concurrent magnesium and potassium supplementation is allowed to maintain levels within a normal range.
- All other nonhematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition.

Hematologic toxicities:

Toxicity	Action
<u>Within-Cycle (day 8 and 15) Dose Modifications</u> • If platelet count < 30×10^9/L or ANC <0.50×10^9/L on treatment days 8 and 15 (for dose adjustments on day 1, see below).	• Hold treatment • Obtain CBC with diff 2x/week until platelet count or ANC have reached goal outlined above • Upon recovery, reinitiate treatment at 1 dose level reduction as per section 6.3.
<u>Dose Modifications for Subsequent Treatment Cycles</u> • ANC < 1.0×10^9/L, platelet count < 75×10^9/L on day 1 of a cycle.	• Hold romidepsin and ixazomib until resolution as per criteria above • Obtain CBC with diff 2x/week until platelet count or ANC have reached goal outlined above • Upon recovery, reinitiate treatment at 1 dose level reduction as per section 6.3. • The maximum delay before treatment may be discontinued is 21 days and at the discretion of the local PI.
• Delay of > 2 weeks in the start of a subsequent cycle due inadequate recovery to goals outlined above.	• Hold romidepsin and ixazomib until resolution as per criteria above • Obtain CBC with diff 2x/week until platelet count or ANC have reached goal outlined above

Toxicity	Action
	• Upon recovery, reinitiate treatment at 1 dose level reduction as per section 6.3. • The maximum delay before treatment may be discontinued is 21 days and at the discretion of the local PI.
• Grade 4 febrile neutropenia or thrombocytopenia	• Hold treatment • Obtain CBC with diff 2x/week until platelet count or ANC have reached goal outlined above • Upon recovery, reinitiate treatment at 1 dose level reduction as per section 6.3.

Non-Hematological Toxicity Dose Reductions Related to Study Drugs (except alopecia)

NCI CTCAE Grade	Romidepsin	Ixazomib
0-1	No change	No change
2-3	Hold until resolved to ≤ Grade 1, then resume at same level	Hold until resolved to ≤ Grade 1, then resume at same level with exceptions as outlined in table "Non-hematological Toxicity Dose Reductions specific to Ixazomib"
Second episode of grade 3 OR First episode 4 toxicity	Hold until resolved to ≤ Grade 1, then resume at 1 dose level reduction as per section 6.3.	Hold until resolved to ≤ Grade 1, then resume at 1 dose level reduction as per section 6.3.
Third episode of grade 3 OR Second episode 4 toxicity	Hold until resolved to ≤ Grade 1, then resume at 1 dose level reduction as per section 6.3. If toxicity occurs at lowest dose level, then treatment should be discontinued	Hold until resolved to ≤ Grade 1, then resume at 1 dose level reduction as per section 6.3 or discontinue based on local PI judgement If toxicity occurs at lowest dose level, then treatment should be discontinued

Non-hematological Toxicity Dose Reductions specific to Ixazomib:

Peripheral Neuropathy	
• New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold study drug until resolution to Grade ≤ 1 or baseline
• 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
• New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug
Rash	
• Grade 2	• Symptomatic recommendations outlined in Section 5.4

Dosage in Patients with Hepatic Impairment

Reduce the starting dose of ixazomib to 3 mg in patients with moderate (total bilirubin greater than 1.5-3 x ULN) or severe (total bilirubin greater than 3 x ULN) hepatic impairment.

Dosage in Patients with Renal Impairment
Reduce the starting dose of ixazomib to 3 mg in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease (ESRD) requiring dialysis. Ixazomib is not dialyzable and therefore can be administered without regard to the timing of dialysis.

6.3 Dose Levels for Dose Reductions for Phase I

Dose level	Romidepsin	Ixazomib
6	14 mg/m^2 D 1, 8, 15	4mg D 1, 8, 15
5	14 mg/m^2 D 1, 8	4mg D 1, 8, 15
4 (Starting dose)	10 mg/m^2 D 1, 8, 15	4mg D 1, 8, 15
3	10 mg/m^2 D 1, 8, 15	3mg D 1, 8, 15
2	10 mg/m^2 D 1, 8, 15	3mg D 1, 8
1	10 mg/m^2 D 1, 8, 15	2.3mg D 1, 8
0	Discontinue	Discontinue

6.4 Protocol Therapy Discontinuation
In addition to discontinuation from therapy related to toxicities as outlined in section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If protocol therapy is interrupted for ≥ 21 days and at the discretion of the local PI.

6.5 Protocol Discontinuation
If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Cycle = 28 days	Screening	On Treatment Cycle 1+ [2]			Every 3, 6 cycles	Safety follow up	Long-term Follow up[4]
Days	-28 days[1]	1	8	15	1	30 days[2,3] post last dose	Every 3 months
Window		± 3	± 3	± 3	± 7	± 7	±15 days
REQUIRED ASSESSMENTS							
Informed Consent	X						
Review subject eligibility criteria	X						
Medical history, Demographics, Diagnosis &Staging	X						
Physical exam	X	X				X	
Vital signs[6], height[6], weight, ECOG Performance status	X	X				X	
EKG[7]	X						
AEs & concomitant medications	X	X				X	
LABORATORY ASSESSMENTS							
Complete Blood Cell Count with diff, plts (CBC)[8]	X	X	C1-3[10]	C1-3[10]		X	
Comprehensive Metabolic Profile (CMP)[9]	X	X	C1-3[10]	C1-3[10]		X	
Mg, LDH	X	X	C1-3[10]	C1-3[10]		X	
HBV sAg, cAb; HCV Ab[11]; HIV screen[12]	X						
Pregnancy test (serum or urine) WOCBP[13]	-14d						
DISEASE ASSESSMENT[11]							
PET/CT Scan[14]	X	pre C3, pre C5			X[14]		[X][4]
Bone marrow biopsy[15]	-60d	post C2 (if BM+, PET-)					
TREATMENT EXPOSURE							
Romidepsin[16]		X	X	X[16]			
Ixazomib[16]		X	X	X[16]			
CORRELATIVE STUDIES (SPECIMEN COLLECTION)							
Archival tissue or mandatory biopsy	X[5]						
PBMC and plasma samples[18]		pre-C1, C3, C5			X[18]		
Whole Blood for somatic baseline[19]		pre-C1					
BANKING SAMPLES (SPECIMEN COLLECTION)[20]							
Whole Blood		Pre-C1					
Serum and Plasma		Pre-C1, C3					
Unstained slides		Pre-C1					
FOLLOW-UP							
Survival status, Additional Cancer Therapy							X

Key to Footnotes

[1]If screening (baseline) labs were performed within 7 days of D1 of treatment, these do not need to be repeated.

[2]A window of 3 days will be applied to all treatment study visits; for safety follow-up visit and tumor imaging, a 7-day window will apply.

[3]A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment. AEs and SAEs will be collected for 30 days after discontinuation of the study drug. See Section 11.2.

[4]Subjects without documented disease progression will be followed for disease progression every 3 months for 2 years. Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 1 year from the time of documented PD or for a total duration of 2 years after initiation of treatment, whichever is sooner.

[5]Archival tissue confirming disease relapse (after initial or any subsequent salvage therapy) is requested at screening. If archival tissue is unavailable or insufficient, a biopsy is mandatory. FFPE for IHC testing, RNA-Seq, WES, and HTS must be available. Verification of sufficient tissue is required prior to C1D1. Biopsy samples will include FFPE and snap frozen tissue for analysis. See CLM for collection, processing, labeling and shipping instructions.

[6]Vital signs to include temperature, blood pressure, heart rate, respiratory rate. Height at screening only.

[7]EKGs will also be obtained if Zofran or other 5-HT3 serotonin receptor antagonists are used as anti-emetics. In this instance, EKGs should be performed at least 2 weeks after initiation of the medication to assess the QT interval

[8] CBC to include white blood cell count, hemoglobin, hematocrit, platelets, differential

[9] CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen, glucose, AST, ALT, total bilirubin, alkaline phosphatase, total protein, albumin, magnesium and lactate dehydrogenase (LDH).

[10] Laboratory assessments for cycles 1-3.

[11]Perform if abnormal transaminases are present

[12] Perform if patient has risk factors for HIV

[13] For women of childbearing potential (WOCBP): urine or serum βhCG, within 14 days prior to study registration. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[14] Tumor imaging to continue pre-Cycle 3 and 5 and then every 3 cycles thereafter until 24 months after initiation of study treatment, and then every 6 cycles, or until disease progression or at time of suspected clinical progression.

[15].Must be performed within 60 days of C1D1. If the bone marrow is positive and the PET is negative for bone marrow uptake, then a confirmatory bone marrow biopsy will be repeatedat the time of first radiographic CR. If the bone marrow is positive and the PET is positive for bone marrow uptake, then a bone marrow biopsy is not required at the time of first CR.

[16] Romidepsin and ixazomib administration per dosing cohort from Phase I. Ixazomib is not given on Day 15 for dose levels 1 and 2. Romidepsin is not given on Day 15 for dose level 5. See 6.3.

[17] [removed]

[18] PBMC and plasma for future MRD assessments at Pre-Treatment C1D1, C3D1, C5D1, and at every timepoint for response assessment.

[19] Whole blood is to be collected at Pre-Treatment C1D1 for somatic baseline.

[20] Whole blood and unstained slides, if available, will be collected prior to treatment on Cycle 1 Day 1. Serum and plasma will be collected prior to treatment on C1D1 and C3D1.

7.1 Screening Evaluations

7.1.1 Within 28 days prior to registration for protocol therapy

- Informed Consent
- Review Subject eligibility criteria
- Medical history
  - Complete medical and surgical history, history of infections, social history, smoking, alcohol and illicit drug use history
- Demographics
  - Age, gender, race, ethnicity, trial awareness question
- Staging (See appendix II)
- Diagnostic pathology specimen
  - From a recently obtained (within 6 months) lymph node biopsy confirming relapsed or refractory disease or
  - Lymph node biopsy (core-needle or excisional) at enrollment in patients without sufficient archived diagnostic tissue
- Office visit with physical exam
- Height, weight
- Vital signs
  - Temperature, blood pressure, heart rate, respiratory rate
- ECOG performance status (See appendix I)
- EKG, 12-lead
- Adverse event (AE) assessment
  - Baseline AEs will be assessed, see section 11 for AE monitoring and reporting
- Concomitant medication review
- Laboratory assessments
  - CBC, CMP, Mg, LDH
  - HBV sAg and cAb, HCV Ab if abnormal transaminases
  - HIV screen if risk factors present
  - (within 14 days) Pregnancy test (urine or serum) for WOCBP
- PET/CT scan
- Diagnostic specimen (FFPE) for correlative studies

7.2 On Treatment Evaluations

7.2.1 Cycle 1+, Day 1

- Laboratory assessments: CBC, CMP, Mg, LDH
  - **Note:** Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.
- Correlative laboratory assessments: see section 7.2.3
- Office visit
- Physical Exam with vital signs and weight
- ECOG performance status
- Adverse event (AE) assessment

- Concomitant medication review
- Drug administration of romidepsin and ixazomib per dosing cohort

7.2.2 Cycle 1+, Day 8 and 15

- Laboratory assessment: CBC, CMP, Mg, LDH for first 3 cycles.
- Drug administration of romidepsin and ixazomib per dosing cohort

7.2.3 Correlative laboratory assessments

- PBMC and plasma for future MRD assessments on C1D1, C3D1, C5D1, and at every time point for response assessment.
- Whole blood is to be collected at Pre-Treatment C1D1 for somatic baseline.
- Archival FFPE or diagnostic biopsy frozen sections for future RNA-Seq, WES, and HTS.
- Archival FFPE or diagnostic biopsy slides for IHC (TNFR2 and HR23B)

7.2.4 Banking Sample Collection

- Whole blood, serum and plasma will be collected prior to treatment on Cycle 1 Day 1
- Serum and plasma will be collected prior to treatment on Cycle 3 Day 1
- Unstained slides will be requested from the subject's pre-treatment tumor sample, if available.

7.2.5 Disease assessment

- PET/CT scan pre-cycle 3 and 5, and then every 3 cycles thereafter until 24 months after initiation of study treatment, and then every 6 cycles, or until disease progression or at time of suspected clinical progression of disease.
- Bone marrow biopsy. If the baseline bone marrow is positive and the PET is negative for bone marrow uptake, then a bone marrow biopsy will be repeated after cycle 2. If the bone marrow is positive and the PET is positive for bone marrow uptake, then a bone marrow biopsy will not be repeated.

7.3 Safety Follow-up Evaluations

A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

- Office visit
- Laboratory assessment: CBC, CMP, Mg
- Physical Exam with vital signs and weight
- ECOG performance status
- Adverse event (AE) assessment
- Concomitant medication review

7.4 Long Term Follow-up Evaluations

All subjects will be followed until documented disease progression. Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months for 2 years.

Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 1 year from the time of documented progression or for a total duration of 2 years after initiation of treatment, whichever is sooner. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

1. *TNFR2 and HR23B expression:* TNFR2 and HR23B expression (at the protein level, by immunohistochemistry) will be examined as predictive biomarkers for response, as overexpression of these proteins have been shown to confer susceptibility to proteasome inhibitors and HDAC inhibitors, respectively. Additional IHC markers may be analyzed.

Future correlative studies:

2. *Examination of the "cell of origin" in PTCL, NOS as a predictive biomarker[39,40,42]:* A significant challenge for PTCL investigators is that the most common PTCL until recently remained "unspecified". We hypothesized that consideration of normal T-cell ontogeny may unveil specific PTCL subtypes with distinct characteristics. Following antigen-receptor signaling, transcription factors direct the differentiation of naïve CD4+ helper T (Th) cells into distinct populations of effector or memory T cells [65]. For example, the transcription factor GATA-3 binds the Th2 cytokine locus and is the "master regulator" of Th2 differentiation[59,66-68]. In addition, GATA-3 regulates the expression of genes implicated in mediating resistance to chemotherapy, and promotes T-cell survival and proliferation[69-71]. We and our collaborators performed gene expression profiling studies in two independent PTCL, NOS cohorts[39,40]. Unsupervised hierarchical clustering revealed two dominant subclusters, one of which is enriched for GATA-3 and its gene targets (i.e. "GATA-3 PTCL"), while the other is enriched for T-bet and its gene targets (i.e. "T-bet PTCL"). In both studies, GATA-3 PTCL, identified by either immunohistochemistry or gene expression profiling, was associated with significantly inferior progression-free and overall survival (OS), and a high rate (>50%) of primary refractory disease. In addition, GATA-3 expression was associated with distinct clinicopathological features, including IL-5-dependent hypereosinophilia and extranodal (predominantly cutaneous) involvement[39]. Therefore, these PTCL, NOS subtypes are likely epigenetically/genetically distinct and may be anticipated to have corresponding differences in their susceptibility to conventional and targeted therapeutic agents. RNA-seq will be performed using diagnostic biopsy specimens. Using this approach, we will determine the cell of origin for PTCL, NOS and examine the extent to which the cell of origin is a predictive biomarker for response. Given the prevalence of PTCL, NOS, we estimate that approximately 30-40% of patients enrolled will have PTCL, NOS. Therefore, we understand that an insufficient number of PTCL, NOS patients may be enrolled to appreciate a small difference in response rates between PTCL, NOS subtypes. While this is a hypothesis-generating aim, we are interested in discerning a large, and potentially practice-changing, difference in response between these subtypes. Nonetheless, this question may require closer scrutiny in future trials.

3. *Evaluation of the depth of response by high-throughput sequencing of the T-cell receptor (TCRβ) third complementarity determining region (CDR3) in patients achieving a CR*[72]*:* Despite the frequent loss of T-cell antigens, expression of the T-cell receptor (TCR) is retained in >90% of PTCL, NOS [reviewed in [73]]. This observation suggests that the TCR may play a pathogenic role in PTCL. In fact, we have found that TCR engagement in primary malignant T cells leads to widespread changes in gene expression and the activation of important transcription factors, including NF-κB and GATA-3 (data not shown). Furthermore, TCR engagement promotes their growth, survival, and resistance to chemotherapy (data not shown). These selective pressures apparently favor maintenance of TCR expression in PTCL and suggest that the TCR is an attractive candidate for MRD monitoring by high-throughput sequencing (HTS). HTS of the third complementarity determining region (CDR3) of the TCRβ or TCRγ genes is able to identify and quantify the relative frequency of clonal T cells in T-cell lymphomas[72,74-77]. This strategy will be exploited to determine the depth of response among patients achieving a complete remission.

4. *Examine the genetic landscape as a predictive biomarker:* Transcriptome sequencing (RNA-seq) and targeted whole-exome sequencing (OncoSeq1500, i.e. sequencing of ≈1700 of the most commonly mutated genes in human cancers), as previously described by our collaborator (A. Chinnaiyan, see http://mctp.med.umich.edu/patients/requesting-tests)[78]. Transcriptome sequencing will be used to identify the clonal TCR for MRD monitoring among complete responders. We anticipate that recurrent mutations in PTCL may be associated with susceptibility or resistance to treatment [42].

8.1.1 Source and Timing of Biospecimen Collections

Tissue Collections
Archival tissue is requested at screening. If archival tissue is unavailable or found to be insufficient, a biopsy is mandatory prior to treatment. Biopsy samples will include FFPE and flash frozen tissue for future analysis. See CLM for collection, processing, labeling and shipping instructions.

Blood Collections
Whole blood will be collected and processed for PBMC's and plasma at C1D1 and every timepoint for response assessment.

Whole blood for future somatic baseline will be collected at pre-treatment C1D1.

8.1.2 Storage of Biospecimens

Patient samples (tissue, blood, serum, plasma) collected for this study will be retained at Big Ten CRC Administrative Headquarters until distributed for analysis. De-identified specimens will be stored indefinitely or until they are used up. If consent for future use of specimens is withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

8.1.3 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

8.1.4 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified Big Ten Cancer Research Consortium studies. Hoosier Cancer Research Network, as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at Cycle 3 Day 1.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at Cycle 3 Day 1.
- Unstained slides: Unstained slides will be obtained from the subject's pre-treatment tumor sample.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.1.5 Confidentiality of Biospecimens

Samples will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will only be identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

Responses will be performed in accordance with the Revised Lugano classification staging system for non-Hodgkin's Lymphoma.

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least 1 cycle(s) of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

9.1 Evaluation of Best Overall Response

Based on definitions provided in section 9.2.

9.2 Definitions for Response Evaluation

Revised Criteria for Response Assessment[79]	
Response and Site	**PET-CT-Based Response**
Complete Lymph nodes and extralymphatic sites	*Complete metabolic response* Score 1, 2, or 3 with or without a residual mass on 5PS* It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal

	mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake
Nonmeasured lesion	
Organ enlargement	Not applicable
New lesions	Not applicable
Bone marrow	None No evidence of FDG-avid disease in marrow
Partial	*Partial metabolic response*
Lymph nodes and extralymphatic sites	Score 4 or 5* with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease
Nonmeasured lesion	Not applicable
Organ enlargement	Not applicable
New lesions	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No response or stable disease	*No metabolic response*
Lymph nodes and extralymphatic sites	Score 4 or 5* with no significant change in FDG uptake from baseline at interim or end of treatment
Nonmeasured lesion	Not applicable
Organ enlargement	Not applicable
New lesions	None
Bone marrow	No change from baseline
Progressive disease	*Progressive metabolic disease*
Lymph nodes	Score 4 or 5* with an increase in intensity of uptake from baseline and/or
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment
Nonmeasured lesion	None
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered
Bone marrow	New or recurrent FDG-avid foci
*5PS = 5 point scale, defined as 1: no uptake above background; 2: uptake ≤ mediastinum; 3: uptake > mediastinum but ≤ liver; 4: uptake moderately > liver; 5: uptake markedly higher than liver and/or new lesions; X: new areas of uptake unlikely to be related to lymphoma.	

9.2.1 Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started) or initiation of new antineoplastic therapy.

9.2.2 Complete Response Rate
The complete response rate is the proportion of all subjects with confirmed CR according to Lugano 2014, from first day of treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the start of treatment) or initiation of new antineoplastic therapy.

9.2.3 Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to Lugano 2014, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment) or initiation of new antineoplastic therapy.

9.2.4 Overall Survival
Overall survival is defined by the date of first treatment to date of death from any cause.

10. DRUG INFORMATION

10.1 Ixazomib (See investigator brochure for additional details) [80]
Ixazomib is a reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.

Ixazomib induced apoptosis of multiple myeloma cell lines in vitro. Ixazomib demonstrated in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. In vivo, ixazomib demonstrated antitumor activity in a mouse multiple myeloma tumor xenograft model.

10.1.1 Supplier/How Supplied
Ixazomib will be supplied by Takeda Oncology at no charge to patients participating in this clinical trial. The ixazomib drug product will be from investigational supply.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Description of Investigational Agent
The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg capsules as the active boronic acid. The 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

For additional details, please see the ixazomib IB.

10.1.3 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. Ixazomib should be stored at the investigative site between +2°C and +30°C (35.6°F-86°F). Do not freeze ixazomib or store above 30°C. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Store capsules at room temperature in original packaging until immediately prior to use.

10.1.4 Handling and Disposal

Ixazomib is a cytotoxic drug. Follow applicable special handling and disposal procedures. Do not open or crush capsules. Avoid direct contact with the capsule contents. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

10.1.5 Dispensing

Ixazomib must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Ixazomib should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.6 Adverse Events

The most common adverse events associated with ixazomib are thrombocytopenia, gastrointestinal toxicity (diarrhea, constipation, nausea, and emesis), peripheral neuropathy, peripheral edema, and cutaneous reactions. Please see package insert for the comprehensive list of adverse events.

10.2 Romidepsin (see package insert for full prescribing information) [81]

Romidepsin is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins, such as transcription factors. In vitro, romidepsin causes the accumulation of acetylated histones, and induces cell cycle arrest and apoptosis of some cancer cell lines with IC50 values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.

10.2.1 Supplier/How Supplied

Commercial supplies of romidepsin will be used in this study and billed to third party payers or the subject.

10.2.2 Preparation

Romidepsin is supplied as a kit including a sterile, lyophilized powder in a 10 mg single-dose vial containing 11 mg of romidepsin and 22 mg of the bulking agent, povidone, USP. In addition, each kit includes a single-dose sterile diluent vial containing 2.4 mL (2.2 mL deliverable volume) of 80% propylene glycol, USP, and 20% dehydrated alcohol, USP.

Romidepsin should be prepared according to the package insert.

10.2.3 Storage and Stability

Romidepsin for injection is supplied as a kit containing 2 vials in a single carton. The carton must be stored at 20° to 25°C, excursions permitted between 15° to 30°C. (See USP Controlled Room Temperature.)

10.2.4 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered as per institutional guidelines.

10.2.5 Dispensing

Romidepsin must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Romidepsin should be stored in a secure area according to local regulations.

10.2.6 Adverse Events

The most likely adverse events from administration of romidepsin include fatigue, electrolyte disturbances, infections, sepsis, gastrointestional toxicity (nausea, anorexia, vomiting, dysgeusia, diarrhea, and constipation), anemia, thrombocytopenia, neutropenia, and weakness. See package insert for the comprehensive list of adverse events.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- New primary malignancy
- Pregnancy

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Serious Adverse Events (SAEs) or Serious Suspected Adverse Reactions (SSARs)

11.2.2.1 Site Requirements for Reporting SAEs or SSARs to Big Ten CRC Administrative Headquarters

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s).
- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form (see Documents/info tab of the EDC) to Big Ten CRC AHQ within **1 business day** of discovery of the event**.** The form will be sent electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved, sites must electronically submit a follow up SAE Submission Form within a reasonable timeframe to Big Ten CRC AHQ at safety@hoosiercancer.org.

11.2.2.2 Site Requirements for Reporting Pregnancy and Birth Events to Big Ten CRC Administrative Headquarters

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the site investigator immediately and permanently discontinue study drug. The site must immediately submit a completed Pregnancy Form to Big Ten CRC AHQ at safety@hoosiercancer.org. 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 (i.e. from the initiation of study drug(s) through 90 days after the last dose of study drug), the site investigator must also immediately submit a completed Pregnancy Form to Big Ten CRC AHQ at safety@hoosiercancer.org. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.2.2.3 Big Ten CRC AHQ Requirements for Reporting SAEs to Takeda Oncology

Big Ten CRC AHQ will report all SAEs to Takeda Oncology within **1 business day** of receipt of the SAE Reporting Form. Follow-up information will be provided to Takeda Oncology as reasonably requested.

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

11.2.2.4 Big Ten CRC AHQ Requirements for Reporting Pregnancy and Birth Events to Takeda Oncology

Big Ten CRC AHQ will report all pregnancy and birth events to Takeda Oncology within **1 business day** of receipt of the Pregnancy Form. Follow-up information will be provided to Takeda Oncology as reasonably requested.

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

11.2.2.5 Product Complaints

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

Phone: 1-844-N1-POINT (1-844-617-6468)
E-mail: GlobalOncologyMedinfo@takeda.com
FAX: 1-800-881-6092
Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

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

11.2.2.6 Sponsor-Investigator Responsibilities

Big Ten CRC AHQ will send a SAE summary to the sponsor-investigator and the Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Investigator Assistance Program (MIAP) **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.2.7 Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Investigator Assistance Program (MIAP) Responsibilities for Reporting SAEs to FDA

MICHR-MIAP is responsible for managing the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. Big Ten CRC AHQ will obtain a copy of the cross reference letter(s) from Takeda and provide to MICHR-MIAP for the IND application (MICHRMIAP@med.umich.edu). MICHR-MIAP will cross-reference this submission to Takeda Oncology 's parent IND at the time of submission. MICHR-MIAP will provide Big Ten CRC AHQ with a copy of the application and Big Ten CRC AHQ will provide a copy of these documents to Takeda Oncology.

MICHR-MIAP will be responsible for all communication with the FDA in accordance with 21CFR312 which includes but is not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. MICHR-MIAP will provide Big Ten CRC AHQ with copies of any FDA communication. Big Ten CRC AHQ will provide a copy of these documents to Takeda Oncology as required per contract.

11.2.2.8 IND Safety Reports Unrelated to this Trial

Takeda Oncology will provide Big Ten CRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. Big Ten CRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. Big Ten CRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). Any changes made to the protocol and/or informed consent document will be submitted to the FDA by MICHR-MIAP. All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from Big Ten CRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

This is a phase I/II multicenter, open label, single arm, non-randomized trial to determine the MTD of ixazomib in combination with romidepsin followed by an initial assessment of efficacy at the MTD in relapsed/refractory PTCL patients.

Phase I. We will estimate the MTD among one of three dose levels of romidepsin plus a fixed dose of ixazomib. We will target a rate of DLT of 0.25 and enroll patients until either (i) 18 have been treated at one dose, and the next enrolled patient would also be assigned to that dose level, or (ii) a total of 36 patients have been enrolled across all dose levels combined. Dose assignments will be made according to the TITE-CRM design[82]. At each dose assignment, we will estimate the one-parameter power model, $Pr(Tox|dose\ j) = (d_j)^{\exp\{b\}}$, where $\{d_4,d_5,d_6\}=\{0.05,0.15,0.27\}$ is the pre-specified skeleton and the parameter b is to be estimated. The next patient will be assigned to dose level j, j=4,5,6, such that the model estimated probability of DLT at that dose level is closest to 0.25 but not exceeding 0.33. Any patients who are free of DLT but have only finished t days of their first cycle, $t < 28$, will have their

likelihood contribution downweighted by a factor ($t^2/28^2$). We will also use the following safety constraints:

1. Dose levels 5 or 6 will not be assigned until at least one patient has completed a single cycle at the lower dose with no DLTs.
2. After the first six patients complete the first cycle, if the estimated rate of DLT at dose level 4 exceeds 0.33, the trial will stop for toxicity.

The estimated MTD is the dose level with a model-estimated rate of DLT closest to 25% (but not more than 33%) after 36 patients have been enrolled (or the dose level where 18 patients have been treated, and the next enrolled patient would also be assigned to that dose level).

The (up-to) 18 patients at the estimated MTD will comprise the interim analysis of a 2-stage phase II study of efficacy of this dual-agent therapy. The patients will be evaluated for CR and comprise an interim futility analysis for the dual-agent therapy. If at least 3 of the (up-to) 18 patients show CR, we will proceed to the second stage of the phase II. If the phase I stage terminates with 18 patients at the estimated MTD, this corresponds to an empiric CR rate of 3/18=17%; if the phase I stage terminates with 16 or 17 patients at the estimated MTD (because total enrollment hits 36 patients), this corresponds to an empiric CR rate of 19% or 18%.

Phase II. Upon successful completion of the phase 1 design/interim efficacy analysis, we will transition to a final evaluation of the efficacy of the dual-agent ixazomib and romidepsin at the MTD. We will test the null hypothesis that the rate of CR is 15%, which is the expected CR rate for romidepsin (see section 1.2). Additional patients will be enrolled to the dual-agent MTD estimated from the phase I step, for a total of up to 30 patients at the MTD (up to 18 from phase 1 + 12 from phase II). When all patients have been followed for response status, if at least 8 patients demonstrate CR, we will declare the dual-agent MTD to be sufficiently efficacious. With 30 patients, this is an empiric CR rate of 27%. If the true CR rate is 0.15, this will occur with probability 0.068 (type I error); if the true CR rate is 0.35, this will occur with probability 0.87 (power). Section 12.3 summarizes the statistical performance of this design in more detail. In the unlikely scenario that fewer than 18 patients are at the MTD after the phase I terminates (the probabilities of this occurring are in Table 12.3.1), we will have slightly reduced power to detect a high CR rate (see Table 12.3.2).

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

See section 2.2

12.2.2 Definition of Secondary Endpoints

See section 2.2

12.3 Sample Size and Accrual

The maximum sample size across both phases will be 48: up to 36 in phase I and 12 additional patients in phase II. Table 12.3.1 provides justification for the phase I sample size. In simulations of eight different dose-toxicity curves, the phase I study identified an acceptable dose level, defined as having true rate of DLT within 0.25 +/- 0.08, with probability between 0.56-0.83 (assuming that at least one

such dose level exists). This probability increases if more than one dose level is considered acceptable or if the true rates of DLT differ more between dose levels.

Table 12.3.1: Phase I Operating Characteristics from 1000 simulated trials. Up to 36 patients are enrolled (unless 18 patients are enrolled to estimated MTD)

True DLT Rates (3 Dose Levels; Acceptable* in **Bold**)	% Trials Estimating **Acceptable** Dose as MTD	% Trials Stopping for Toxicity	% Trials Enrolling < 18 at Estimated MTD	# Patients Enrolled to Estimated MTD: 5th Percentile	Total # Patients Enrolled: (5th, 95th) Percentile
{0.10,0.11,**0.33**}	63%	0.3%	12.8%	15	(22,36)
{0.10,0.15,**0.20**}	77%	0.4%	5.4%	17	(22,36)
{0.13,**0.30,0.32**}	83%	0.7%	7.6%	17	(21,36)
{0.15,**0.18**,0.37}	56%	2.2%	11.5%	15	(21,36)
{0.15,**0.25**,0.52}	76%	1.8%	7.7%	16	(21,36)
{**0.20,0.23**,0.39}	75%	4.6%	7.4%	17	(19,36)
{**0.26,0.33**,0.43}	80%	14.1%	6.9%	17	(19,36)
{0.36,0.45,0.57}	--	46.2%	5.2%	17	(19,36)
*Acceptable dose levels have true rates of DLT within 0.25 +/- 0.08					

Table 12.3.2 provides justification for the phase II sample size of 12 additional patients. The phase II stage will power at least 0.80 to detect a CR rate at the estimated MTD of 0.35, as long as at least 16 patients from phase I are at the estimated MTD, which would yield a total sample size of 28.

Table 12.3.2: Phase II Operating Characteristics from 1000 simulated trials. Up to 30 patients are enrolled. The futility analysis proceeds if at least 3 patients demonstrate CR, and the MTD is found to be efficacious at the final analysis if at least 8 patients demonstrate CR.

True CR rate at MTD	# Patients to MTD in Phase I (+Phase II)	% Trials Stopping for Futility	% Trials Finding MTD to be Inefficacious	% Trials Finding MTD to be Efficacious (Type I error – Power)
0.15	18(+12)	48%	45%	6.8%
0.15	17(+12)	52%	42%	5.7%
0.15	16(+12)	56%	39%	4.7%
0.25	18(+12)	14%	39%	48%
0.25	17(+12)	16%	40%	44%
0.25	16(+12)	20%	41%	39%
0.35	18(+12)	2.4%	11%	87%
0.35	17(+12)	3.3%	12%	84%
0.35	16(+12)	4.5%	15%	81%

Patients who withdraw their consent during either stage of the study prior to the first response assessment will be replaced.

Accrual is anticipated at 2 patients per month, which implies study duration of 3 years, allowing for up to 1 year of follow-up for the final enrolled patient.

12.4 Analysis Datasets

The primary Safety population will be the up to 36 patients enrolled in the phase I stage. The secondary Safety population will be all enrolled patients from phase I or phase II (up to 48 patients total), which will be used for AE reporting. The Efficacy population will be the up-to 30 patients from phase I or phase II who are treated at the estimated MTD.

12.5 Assessment of Safety

The MTD will be estimated from the primary safety population, as described in Section 12.1. The overall safety will be characterized with the secondary Safety population. Any subject that receives at minimum one dose of treatment will be evaluable for toxicity. The NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4 will be used to assess toxicities. Refer to Section 7 (Study calendar) for the schedule of toxicity assessments.

12.6 Assessment of Efficacy

Only patients who have received at least 1 cycle(s) of therapy, and have had their disease re-evaluated will be considered evaluable for response. Non-evaluable patients will be replaced.

12.7 Data Analysis Plans

12.7.1 Analysis Plans for Primary Objectives

See Sections 12.1 and 12.3

12.7.2 Analysis Plans for Secondary Objectives

ORR at one year will be summarized for the Efficacy population, including appropriate uncertainty. DOR in the Efficacy population will be summarized via Kaplan-Meier (KM) methods and confidence intervals, with time = 0 defined as the date of first response. TTNT and OS will also be summarized with KM methods, with time = 0 defined as the date of first dose of cycle 1.

12.7.3 Analysis Plans for Exploratory Objectives

The association between TNFR2 and HR23B expression and efficacy (CR, OR, DOR, or OS) will be summarized via appropriate statistical measures of correlation.

12.8 Interim Analysis/Criteria for Stopping Study

The TITE-CRM methodology automatically incorporates stopping rules for safety during dose escalation. Specifically, the trial will stop for safety if the model-estimated rate of DLT at dose level 4 ever exceeds 0.33. A single interim futility analysis will be conducted after the phase I stage concludes. Specifically, we require that at least 3 patients among those assigned to the final estimated MTD demonstrate CR by at least 1 year in order to proceed to the phase II stage. Sections 12.1 and 12.3 provide more details. Oversight will also be provided by the DSMC.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The Data and Safety Monitoring Committee (DSMC) of The University of Michigan Rogel Cancer Center is responsible for monitoring the safety and data integrity of the trial.

Big Ten CRC AHQ oversight activities include:

- Review and process all adverse events requiring expedited reporting as defined in the protocol
- Provide timely reports to MICHR-MIAP (MICHRMIAP@med.umich.edu) that require expedited reporting
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator and MICHR-MIAP
- Coordinate weekly study team meetings for the phase I portion of the trial and then monthly meetings during the phase II portion. These meetings will include each accruing site's principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion).
- Monthly during the phase I portion and quarterly during the phase II portion, the study team meetings will also discuss matter related to:
  - Enrollment rate relative to expectations, characteristics of participants
  - Safety of study participants (Serious Adverse Event reporting)
  - Adherence to protocol (protocol deviations)
  - Completeness, validity and integrity of study data
  - Retention of study participants
- These meetings are to be documented by the site data manager or study coordinator using the Protocol Specific Data and Safety Monitoring Report (DSMR), signed by the site principal investigator or designated co-investigator. Big Ten CRC AHQ will assist in this process. The DSMR can be found in the Documents/info tab of the EDC. Each site is required to submit the completed DSMR to Big Ten CRC AHQ on a monthly basis during the phase I portion and a quarterly basis during the phase II portion together with other pertinent documents for submission to the DSMC.

13.2 University of Michigan's Data Safety Monitoring Committee

The DSMC will review the information included on the DSMRs from the first subject enrolled until the last subject has completed the study drug interventions. Documentation of DSMC reviews will be provided to sponsor-investigator and Big Ten CRC AHQ. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with Big Ten CRC AHQ and MICHR-MIAP to address the DSMC's concerns.

The DSMC will provide the sponsor-investigator and Big Ten CRC AHQ evidence of its review. Big Ten CRC AHQ will distribute this information to the participating sites for submission to their respective IRB per the local IRB's policies and procedures.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. The study site personnel will make corrections.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site

investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Takeda Oncology or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. MICHR-MIAP will be responsible for submitting FDA Form 3674 to the FDA. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

Big Ten CRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through the web-based clinical research platform compliant with Good Clinical Practices and Federal Rules and Regulations. Big Ten CRC AHQ personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or another secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, per study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/ Big Ten CRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and

retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until Big Ten CRC AHQ confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, Takeda Oncology, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects' identities will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to Big Ten CRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require. The site investigator must submit all IRB approvals Big Ten CRC AHQ.

Progress reports and notifications of adverse events will be provided to the IRB per local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will comply with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16. APPENDICIES

I. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale
II. Revised Staging System for Primary Nodal Lymphomas (Lugano Classification)
III. Inhibitors and inducers of CYP3A4/5

APPENDIX I: Eastern Cooperative Group (ECOG) Performance Status Scale[83]

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX II: Revised Staging System for Primary Nodal Lymphomas

Non-Hodgkin Lymphoma – Revised staging system (Lugano classification)[79]		
Stage	Involvement	Extranodal (E) Status
Limited Stage		
I	Single lymph node region or lymphoid structure (i.e. spleen, thymus, Waldeyer's ring)	Single extranodal lesions without nodal involvement
II	Two or more node regions on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II Bulky*	Stage II as above with "bulky" disease	N/A
Advanced Stage		
III	Lymph node regions or structures on both sides of the diaphragm; nodes above the diaphragm with splenic involvement	N/A
IV	Additional noncontiguous extralymphatic involvement	N/A
* Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors		

APPENDIX III: Inhibitors and inducers of CYP3A4/5

Examples of inhibitors and inducers of CYP3A4/5 can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx[64]

The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website on May 28, 2015.

- A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance.
- A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.
- A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20-50% decrease in clearance.

Inhibitors of CYP3A4/5	
Strong inhibitors:	**Other inhibitors:**
Indinavir	Amiodarone
Nelfinavir	Chloramphenicol
Ritonavir	Boceprevir
Clarithromycin	Ciprofloxacin
Itraconazole	Delaviridine
Ketoconazole	Diehtyl-dithiocarbamate
Nefazodone	Fluvoxamine
Saquinavir	Gestodene
Suboxone	Imatinib
Telithromycin	Mibefradil
	Mifepristone
Moderate inhibitors:	Norfloxacin
Aprepitant	Norfluoxetine
Erythromycin	Starfruit
Diltiazem	Telaprevir
Fluconazole	Voriconazole
Grapefruit juice	NOT azithromycin (unique in that it does not inhibit CYP3A4)
Seville orange juice	
Verapamil	
Diltiazem	
Weak inhibitors:	
Cimetidine	

Inducers of CYP3A4/5	
Efavirenz	Phenobarbital
Nevirapine	Phenytoin
Barbiturates	Pioglitazone
Carbamazepine	Rifabutin
Glucocorticoids	Rifampin
Modafinil	St. John's wort
Oxcarbazepine	Troglitazone

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