TACL

Therapeutic Advances in
Childhood Leukemia & Lymphoma

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Activated:

TACL
Therapeutic Advances in
Childhood Leukemia and Lymphoma

A TACL Phase 1/2 Study of PO Ixazomib in Combination with Chemotherapy for Childhood Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

IND# 140730

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Changes from Previous Version: ☐ N/A

Section(s)	Revisions Made	Rationale
2.4.1	• Removed section 2.4.1 as it has been replaced with this Changes from Previous Version table	• Update
6.1.4	• Updated Toxicity/Adverse Events to reflect recent updates in the Ixazomib Investigator's Brochure edition 15	• Update
15.0	• Updated Potential Discomforts and Risks of Ixazomib to reflect new risk of bronchitis as stated in the Ixazomib Investigator's Brochure edition 15	• Update

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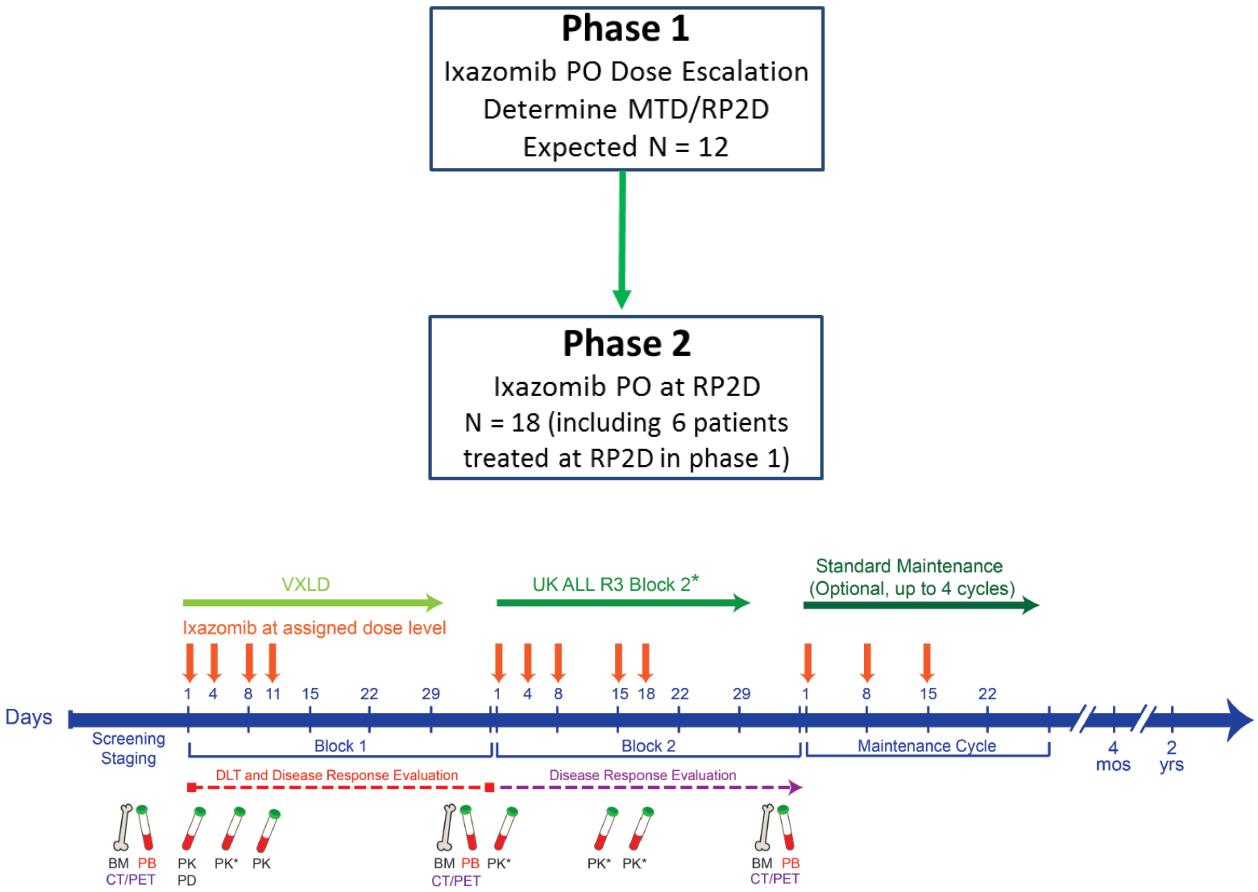
STUDY SCHEMA



Bone Marrow Evaluation: pre-study (all patients); end of block 1 – all leukemia patients and only lymphoma patients whose MRD was positive at the study entry; end of block 2 – all patients with bone marrow disease (including positive MRD) at end of block 1.

PK Studies: Phase 1: Two mL blood samples will be collected at different time points on Days 1 and 11 in block 1. Phase 2: Sparse PK sampling will be conducted on Days 1, 8, and 11 in block 1 and Days 1, 15, and 18 in block 2. The PK sampling schedule is listed in protocol section 8.3. *indicates PK samples collected only in phase 2.

PD Studies: Block 1, Day 1 – Five mL blood sample at 3 time points: prior to start of chemotherapy, at 4-6 hours and 24 hours following the first ixazomib dose for patients over 12 kg. If under 12 kg, three mL blood samples drawn at 2 time points: prior to start of chemotherapy and 4-6 hours after the first ixazomib dose.

*indicates that block 2 therapy is not required for patients who achieve CR/CR MRD-/ CRi after block 1 therapy at their assigned dose level. These patients will have the option of continuing with block 2 therapy, moving directly on to the maintenance cycle, or going off protocol therapy. Any patients who have PR/SD will continue with block 2 therapy.

1.0 GOALS AND OBJECTIVES

1.1 Primary Objectives for Phase 1

1.1.1 Determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of PO ixazomib administered in conjunction with block 1 re-induction chemotherapy in children with relapsed/refractory ALL or lymphoblastic lymphoma (LLy)

1.1.2 Define and describe the toxicities of PO ixazomib in combination with block 1 re-induction chemotherapy in children with relapsed/refractory ALL or LLy

1.1.3 Characterize the pharmacokinetics (PK) of PO ixazomib in combination with block 1 re-induction chemotherapy in children with relapsed/refractory ALL or LLy

1.2 Primary Objective for Phase 2

1.2.1 Estimate the rate of overall response (CR + CR MRD- and CR + CR MRD- + CRi) after block 1 re-induction chemotherapy in patients with multiply relapsed/refractory ALL or LLy

1.3 Secondary Objective

1.3.1 Describe toxicities occurring in patients receiving PO ixazomib with block 2 re-induction chemotherapy after achieving CR/CR MRD-/CRi with PO ixazomib + VXLD

1.3.2 Assess the palatability and acceptability of the liquid oral ixazomib in children with multiply relapsed/refractory ALL or LLy

1.4 Exploratory Objectives

1.4.1 Evaluate the pharmacodynamic (PD) properties of ixazomib, including determination of proteasome activity and effects of proteasome inhibition on cell stress proteins including the unfolded protein response

1.4.2 Assess the tolerability of ixazomib in combination with maintenance chemotherapy

1.4.3 Describe the rate of CR + CR MRD- and CR +CR/MRD- + CRi after block 2 re-induction chemotherapy

1.4.4 Describe EFS and OS at 4 months and 2 years in both phase I and 2 cohorts of patients

1.4.5 Describe the proportion of the subjects with ALL who achieve MRD status < 10^{-3} and < 10^{-4} by flow cytometry after block 1 and block 2 re-induction chemotherapy

2.0 BACKGROUND

2.1 Introduction and Rationale for Development

Despite ongoing progress in improving event-free survival (EFS) for patients with acute lymphoblastic leukemia (ALL),[1,2] nearly 15–20% children will relapse. Outcomes after relapse have not changed in 20 years and remain poor despite intensive chemotherapy and hematopoietic stem cell transplant.[3]

In multiple studies, bortezomib, a proteasome inhibitor, has shown the ability to potentiate the anti-tumor effects of standard cytotoxic chemotherapy in childhood leukemia.[4] Currently, another proteasome inhibitor, carfilzomib, is being tested in combination with chemotherapy by TACL (NCT02303821). Ixazomib is a new proteasome inhibitor, with both intravenous (IV) and oral (PO) formulations, that has been approved by the FDA to treat patients with multiple myeloma (MM).[5] Similar to bortezomib, ixazomib selectively inhibits the β5 site of the 20S proteasome and also demonstrates synergistic activity with dexamethasone and doxorubicin in multiple myeloma.[6] In preclinical studies, ixazomib has shown increased potency and superior efficacy over bortezomib because it has a shorter proteasome dissociation half-life that leads to a higher tumor-to-blood ratio of proteasome inhibition.[7-9]

The advantage of ixazomib over either bortezomib or carfilzomib is the PO formulation. Currently, no other oral proteasome inhibitor is approved**.** With the development of new promising immunotherapies (CD19 CAR T-cells, blinatumomab, inotuzumab, etc.) in pediatric ALL, the best use for ixazomib in childhood leukemia would be as a PO formulation to intensify maintenance therapy in a subset of newly diagnosed high risk patients in order to improve outcome. This study provides a unique opportunity to utilize an oral formulation of ixazomib as part of a multi-agent re-induction regimen and optional maintenance chemotherapy for patients who have achieved CR/CR MRD-/CRi.

We propose a phase 1 study to estimate the maximum tolerated dose (MTD) of the PO formulation, followed by a screening phase 2 study to investigate the efficacy of ixazomib in combination with chemotherapy in children with relapsed ALL and LLy. The single arm, screening phase 2 design will allow us to use a minimal number of patients to obtain preliminary information about treatment efficacy. After the block 1 chemotherapy if CR/CR MRD-/CRi is achieved, patients will have the option to receive block 2 intensive chemotherapy or maintenance chemotherapy with ixazomib. In addition, we will include a palatability study of oral formulation of ixazomib. Infants and patients with Down syndrome (DS) will be included in this study. However, since they have their unique biology and toxicity profile, infants and DS patients will be in a different stratum and not be included in the primary DLT or response evaluation.

Discovering a safe and tolerable dose of ixazomib in a PO formulation and the preliminary efficacy data will significantly increase the possibility of ixazomib moving forward in frontline pediatric treatment protocols in both intense chemotherapy courses and maintenance courses.

2.2 Introduction of Ixazomib

2.2.1 Ubiquitin-proteasome pathway

The ubiquitin-proteasome pathway (UPP) is essential for the degradation of most short-lived and many long-lived intracellular proteins in eukaryotic cells.[10] Proteasome inhibition stabilizes many cell cycle-dependent proteins that are overexpressed in leukemia cells.[11] Previous studies have shown that proteasome inhibition may sensitize malignant hematologic cells to apoptosis induced by both radiation and chemotherapy.[12,13] Apoptosis following proteasome inhibition is seen in leukemia cell lines[4,14,15] as well as in primary ALL lymphoblasts[4] and mouse leukemia xenografts[16] but not in normal hematopoietic progenitors.[17,18] Important regulatory proteins affected by inhibition

of the UPP system include NF-κB, p53, Bax and other cell regulatory proteins such as the cycle-independent kinase inhibitors p27 and p21.[19] It is believed that proteasome inhibition alters the ratio of pro-apoptotic and anti-apoptotic proteins within the cell, resulting in the increase in the sensitivity to apoptosis.[20]

In addition to constitutive proteasomes, which are responsible for the degradation of major cellular proteins, immune cells also express immunoproteasomes, which are responsible for processing antigens for presentation on major histocompatibility class (MHC) 1 molecules. In general, cells with a hematologic origin (i.e., leukemic cells) express higher amounts of immunoproteasomes compared to constitutive proteasomes.[21] The immunoproteasome catalytic subunits β1i, β2i, and β5i replace the β1, β2, and β5 subunits of the constitutive proteasome.[21] Proteasome inhibitors have demonstrated different selectivity for these catalytic subunits.[9] Data indicates that sensitivity to proteasome inhibition is related to the ratio of immunoproteasomes to proteasomes in leukemia cells.[22]

2.2.2 Overview of Ixazomib

Ixazomib is a peptide boronic acid proteasome inhibitor with both intravenous (IV) and oral (PO) formulations. In 2015, ixazomib was approved by the FDA for the treatment of patients with MM who have received at least 1 prior therapy. It was granted conditional marketing authorization in the EU for the same indication in 2016.

Like bortezomib, ixazomib selectively and reversibly inhibits the β5c and β5i subunit of the 20S proteasome. It has been tested in a panel of > 70 hematologic cell lines, which included 5 pediatric ALL cell lines. The IC_{50} of ixazomib in pediatric ALL lines ranged from 14-37 nM at 48 hours (Study E0246-U1616, manuscript in preparation). These results are similar to those reported for bortezomib sensitivity in pediatric ALL lines.[4,16] In addition, ixazomib has shown antitumor activity in a pediatric T-ALL derived xenograft model.[23]

In vitro, ixazomib showed a shorter proteasome dissociation half-life and greater reversibility of proteasome inhibition compared with bortezomib.[7] The difference in reversibility also applies to the *in vivo* setting. In mice, the ixazomib MTD is higher than that for bortezomib and the compounds show different ratios of blood-to-tissue distribution. When dosed at their respective MTDs, ixazomib demonstrates higher levels of proteasome inhibition in xenograft tumors and lower levels of blood proteasome inhibition than does bortezomib. Furthermore, this difference in blood-to-tumor ratio corresponded with improved antitumor activity of ixazomib in several xenograft models.[7-9] These pharmacologic differences warrant the investigation of ixazomib in pediatric ALL.

2.2.3 Adult studies

Ixazomib has been or is currently being evaluated in a total of 23 clinical studies in adults with relapsed/refractory and newly diagnosed MM, lymphoma, and amyloidosis as follows:

- Eleven completed phase 1 clinical studies investigating the PK, PD, safety, and tolerability of ixazomib; relative bioavailability and food effect; absorption, distribution, metabolism, and excretion; the effect of renal and hepatic impairment on ixazomib PK, and drug-drug interactions.
- Five phase 2 (including phase 1/2) studies, of which 2 are completed and 3 are ongoing
- Seven phase 3 studies, including 1 completed in patients with MM and 6 ongoing (5 in MM, and 1 in amyloidosis)

To date, no clinical studies have been conducted with ixazomib in patients with pediatric ALL. However, there have been 3 investigator-initiated studies of ixazomib in adult patients with ALL.

Phase 1 study of ixazomib as a single agent in adults. Adult phase 1 studies have demonstrated that the MTD of ixazomib is schedule and formulation dependent. When administered twice-weekly for two weeks in a 21 day cycle, the MTD of the IV and the PO formulation is slightly different. The drug related adverse events (AEs) and half-life between the two formulations are similar. Details are presented in Table 1 below.

Table 1: MTD and Dose limiting toxicity (DLT) of ixazomib in adult patients

Reference	**Smith et al., 2015**[24]	**Richardson et al., 2014**[25]
Formulation	IV	PO
Disease	Non-hematologic malignancies[24]	Multiple myeloma
MTD	1.75 mg/m^2	2.0 mg/m^2
DLT	5 out of 22 • Gr 3 rash (1.0 mg/m^2, 1.76 mg/m^2) in two patients • Gr 4 thrombocytopenia (2.34 mg/m^2) • Gr 3 thrombocytopenia with Gr 1 rectal hemorrhage (2.34 mg/m^2) • Gr 3 acute renal failure (2.34 mg/m^2)	2 out of 26 • Gr 3 rash (2.34 mg/m^2) • Gr 4 thrombocytopenia (2.34 mg/m^2)
≥ 5% Drug related Gr ≥ 3 AEs		
Thrombocytopenia	23%	37%
Neutropenia	N/A	17%
Skin/subcutaneous	16%	8%
Fatigue	9%	7%
Dehydration	6%	N/A
Lymphopenia	5%	5%

Adult phase 1/2 studies of Ixazomib in combination with other chemotherapy agents. Kumar et al. used PO ixazomib in combination with lenalidomide and dexamethasone in 65 adult patients with newly diagnosed MM.[26] Ixazomib was given orally on days 1, 8, and 15, lenalidomide was given daily for 21 days, and dexamethasone at 40mg was given weekly on a 28 day cycle. The RP2D of ixazomib was 2.2 mg/m^2. Gr 3 or higher AEs related to any drug were reported in 63% patients, including skin and subcutaneous tissue disorders (17%), neutropenia (12%), thrombocytopenia (8%), and drug-related peripheral neuropathy (6%).

2.2.4 Pediatric Studies

No pediatric studies have been performed.

2.3 Chemotherapy Backbone Rationale

The encouraging data of bortezomib in pediatric ALL and the improved proteasome inhibition by ixazomib lead us to consider a phase 1/2 study using ixazomib in combination chemotherapy in children with relapsed/refractory ALL. UK ALL R3 block 1 chemotherapy (vincristine, dexamethasone, asparaginase, and mitoxantrone) has been widely used to treat children with relapsed/refractory ALL/LL.[27] However, when

it was used in the new agent combination trials in TACL and COG, severe adverse events including life threatening infections were identified.[28,29] Therefore, in this trial, we will use the VXLD backbone (vincristine, dexamethasone, asparaginase, doxorubicin), an effective backbone widely used in ALL therapy with a more favorable toxicity profile. This is the similar backbone used in the TACL 2005-003 study as well as the COG AALL07P1 study.[30,31]

Infants are included in this study. In previous COG infant study AALL0631, excessive life-threatening infection is associated with induction chemotherapy, which resulted in dose reduction.[32] In this protocol, the cytotoxic chemotherapies will be reduced to 80% in infants ≧ 6 months and < 1 year of age; there is further dose reduction of 12% in infants < 6 months of age (total dose 68% of dose in children). This is consistent with the COG AALL0631 study and the new COG infant AALL15P1.

If patients achieve CR/CR MRD-/CRi after block 1, they will have the option of continuing with block 2 therapy, or moving directly on to the maintenance cycle for up to 4 cycles, or going off protocol therapy. If patients have PR/SD, they will continue with block 2 therapy. After completion of block 2 therapy, subjects with CR/CR MRD-/CRi/PR can participate in the optional maintenance cycle for up to 4 cycles.

The block 2 chemotherapy backbone is based on the UK ALL R3 regimen's block 2 (consolidation) schedule[27]. This will be done to obtain further information on toxicity and estimate whether additional ixazomib can further improve the CR + CR MRD- rate. This block is commonly used in the treatment of relapsed ALL and had been safely combined with bortezomib in a similar to block 2 therapy in the COG AALL07P1 study.[9,10] The toxicities defining the DLT will only be evaluable during the block 1 therapy, but severe toxicities will be further assessed in block 2 to determine if ixazomib is tolerable with UK ALL R3 consolidation.

2.4 Ixazomib Dosing and Study Design Rationale

PO formulation of ixazomib will be used in this study. Since ALL is a rapidly growing and aggressive disease, we will use bi-weekly dosing of ixazomib, administering on days 1, 4, 8, & 11 of block 1, and days 1, 4, 8, 15 &18 of block 2 therapy in order to better achieve prolonged proteasome inhibition. This dosing schedule was used in TACL 2005-003[30,31] and COG AALL1231 (NCT02112916) using bortezomib in combination with chemotherapy. In the optional maintenance block, ixazomib will be given in a weekly basis (three weeks on, one week off) on days 1, 8, and 15.

In the phase 1 portion of the study, we will include any patients with relapsed ALL or LLy. A 3+3 design[33] will be used to determine a MTD and/or RP2D for the PO ixazomib in combination with VXLD. For patients without Down Syndrome (DS) and no younger than 1 year of age (the primary stratum), the starting dose will be 80% (1.6 mg/m^2/day) of the adult twice weekly PO MTD (2mg/m^2/day),[25] and one dose level increase to the adult MTD. PK, PD, and toxicity information will be collected.

If an RP2D is established, a phase 2 expansion will be performed at the RP2D. Patients satisfying the phase 2 eligibility criteria (i.e., patients with B-cell ALL/LLy who have failed one or more therapeutic attempts and any patients with relapsed T-cell ALL/LLy) will be enrolled and treated at the RP2D until 18 response evaluable patients have been treated at the RP2D or until a total of 24 evaluable patients overall are enrolled (the total of DLT evaluable patients during phase 1 and response evaluable patients during the phase 2 expansion), whichever occurs first. Response-evaluable patients treated at the PO RP2D in phase 1 will be included in the phase 2 analysis.Infants (< 1 year of age) and patients with DS will be included in phase 1 and 2 of the study. Due to the unique biology and toxicity profile of those patients, they will be in a separate stratum and not be included in the DLT or response evaluation for the primary stratum. To ensure the safety of these patients, they will be entered at one dose level below a determined safe dose level in older, non-DS children, and will follow a 3+3 dose escalation design for safety, although there is no

expectation that this dose escalation will be completed. At no time will the dose given to infants or DS patients exceed the currently established safe dose in non-infant/non-DS patients. For the Phase 2 portion of the study, DS patients will be enrolled at 1.6 mg/m^2/day, which is one dose level lower than the RP2D of ixazomib in non-DS patients (2 mg/m^2/day). These patients will receive leucovorin rescue after intrathecal methotrexate or triple intrathecal chemotherapy. We estimate there will be very few infants and Down syndrome patients enrolled in the study.

2.5 Correlative Biology Studies

The goal of these correlative studies is to determine if changes in proteasome function or cell stress protein expression patterns can predict ixazomib response and drug resistance. The primary aims of these correlative studies are: (1) to delineate the mechanisms of ixazomib action and resistance, and to determine if proteasome alterations correlate with clinical response; and (2) to determine if protein cell stress pathways or other signal transduction pathways identified using reverse phase protein lysate arrays (RPPA) predict response or resistance for the ixazomib + chemotherapy regimen.

2.5.1 Evaluating Mechanisms of Ixazomib Response and Mechanisms of Ixazomib Resistance.

The central hypothesis is that activation of the unfolded protein response (UPR), or induction of other protein cell stress pathways, can predict chemotherapy response, and ultimately clinical outcome. Work from the Cloos and Horton labs have shown that response to proteasome inhibitor therapy is increased in patients that have a high immunoproteasome to constitutive proteasome ratio, both in primary cells and in children treated with the proteasome inhibitor bortezomib.[22,34] Additional details are included in Section 7.2 and Section 8.

2.5.2 Evaluation of Protein Expression and Unfolded Protein Response

Using reverse-phase protein lysate array (RPPA) technology we can globally assess the effects of targeted anti-cancer agents on the proteome by studying protein expression and phosphorylation of over 200 proteins using as few as 200,000 leukemia cells. While previous work in adult AML has demonstrated that functional proteomic profiling can predict treatment response and survival.[35] This correlation has not yet been made in pediatrics. Recent data from the Horton and Kornblau labs has shown that RPPA data correlates with leukemia subtype and vital status (submitted manuscripts).[36-38] RPPA signals following bortezomib with chemotherapy treatment and clinical response are being assessed in two ongoing phase 3 COG clinical trials. We hypothesize that functional proteomic profiling and analysis of the unfolded protein response (UPR) will allow us to 1) further characterize the protein pathways leukemia cell response to ixazomib + chemotherapy treatment, and 2) help to identify biomarkers of either clinical response or therapy resistance. Potential targets include the NF-κB pathway and pathways controlled by the ubiquitin-proteasome pathway which regulates how rapidly leukemia cells multiply, die or mature.[39] Proteasome inhibitors are known to block NF-κB activation, and to trigger the UPR, suggesting that this may be a means of selectively enhancing ixazomib targeting.

2.6 Palatability of Oral Ixazomib Study

Patient acceptance of medication (acceptability) can be defined as the overall ability of the patient to use the medicine as intended. Acceptability of an oral medication is an important consideration in patients, especially children, because it is likely to have a significant impact on the patient's adherence.[40,41] It is even more critical for a medication that is intended to be administered chronically (such as in ALL maintenance therapy). Palatability is one of the main elements of patient acceptability and included tablet/capsule size,

physical burden of dose (number of pills or dosing volume), and the appearance, smell, taste, after-taste and texture of the oral preparations.[42] It is determined by the characteristics of the user and the medication. For pediatric drug development, it is important to consider palatability at the early stage of clinical trials to allow time for pharmaceutical companies to optimize children-friendly formulation. Palatability tests have been performed in several pediatric medications using different measurement scales.[42] In this study, we will incorporate a questionnaire with questions related to the taste and smell using a 5-point facial hedonic scale. This scale allows for indication of preference by pointing at a pictorial scale of facial expressions that has been commonly used in palatability studies.[42,43]

3.0 PATIENT ELIGIBILITY CRITERIA AND ENROLLMENT

3.1 Patient Reservation/Registration

Investigators should consult the Member's Section of the TACL web site to determine if the study is currently open for accrual before approaching patients for participation. Before enrolling a patient on the study, the patient must first be registered with TACL and a reservation must be made with the TACL Operations Center. In order to register the patient and make a reservation, you may call (323) 361-5132 or send an email to tacl@chla.usc.edu with the following information (if sending an email, please put "Reservation Request" in the subject line):

- Study for which you want to make a reservation:
- Name of the institution requesting reservation with contact information
- Patient Initials (Last, First)
- Patient month and year of birth

Each patient will be assigned a unique TACL registration number. If an enrollment slot is available, you will receive an email from the TACL Operations Center to confirm your reservation. All reservations are good for 5 full calendar days starting with the next full day after the day the reservation is made. It is allowable to enroll a patient that has received IT ARA-C, IT MTX or triple IT therapy within 7 days of enrollment as part of their evaluation to diagnose disease relapse.

3.2 Enrollment

An enrollment guide is available on the web site (https://tacl.chla.usc.edu). Patients must be enrolled prior to beginning treatment on this study. Patients will be enrolled by contacting the TACL Operations Center Monday through Friday, 8:30 am – 5:00 pm Pacific Time at (323) 361-5132, except holidays. You will be asked to complete the eligibility form prior to making your call. In addition, the supporting documentation, which confirms eligibility, should be faxed or emailed to the TACL Operations Office.

Each patient will be assigned a study subject number. An email confirming eligibility and assigned dose level will be sent to the treating facility, Study Chair, and Study Vice-Chair. No patient should be enrolled or started on protocol treatment until the enrollment confirmation e-mail has been received from the TACL Operations Office. Enrolled patients should begin treatment within 3 calendar days of study enrollment.

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3.3 Inclusion Eligibility Criteria

The eligibility criteria listed below are interpreted literally and cannot be waived.

3.3.1 Age

Patients must be < 22 years of age at the time of enrollment*.

a) Phase 1 – Initial enrollment will be restricted to patients < 18 years of age until 9 such patients are enrolled

b) Phase 2 – Initial enrollment will be restricted to patients < 18 years of age until 6 such patients are enrolled (applies to Stratum A only)

*Change made for clarification in Phase 2 that patients 21 years of age prior to their 22nd birthday are eligible

3.3.2 Diagnosis

Patients must have a diagnosis of relapsed/refractory ALL or LLy with or without extramedullary disease (including CNS2 and CNS3). Patient with mixed phenotype ALL or mature B (Burkitt-like) leukemia are not eligible.

a) Patients with ALL must have ≥ 5% blasts by morphology.

b) Patients with LLy must have measurable disease documented by clinical, radiologic or histologic criteria (see Section 11)

3.3.3 Performance Level

Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50% for patients ≤ 16 years of age. (See Appendix I for Performance Scales)

3.3.4 Prior Therapy

A. Prior therapeutic attempts

- **Phase 1 –** Any patients with relapsed/refractory ALL or LLy
- **Phase 2**
  1. B-cell ALL/LLy: all patients must have failed one or more therapeutic attempts.
  2. T-cell ALL/LLy: all patients must have failed one or more therapeutic attempts.

B. Recent prior chemotherapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

- **Myelosuppressive chemotherapy:** At least 14 days must have elapsed since the completion of myelosuppressive therapy. However patients may receive any of the following medications within 14 days without a "wash-out" period: Hydroxyurea – Hydroxyurea can be initiated and/or continued for up to 24 hours prior to the start of protocol therapy.
- **"Maintenance-style" therapy** – Therapy including vincristine (dosed a maximum of one-time weekly), oral 6-mercaptopurine, oral methotrexate (dosed a maximum of one-time weekly), dexamethasone (dosed at ≤ 3 mg*/m^2/dose twice daily), and prednisone (dosed at ≤ 20 mg*/m^2/dose twice daily) can be initiated and/or continued for up to 24 hours prior to the start of protocol therapy.
  *Doses can be rounded to adjust for pill size

C. Hematopoietic stem cell transplant: Patients who have experienced their relapse after a HSCT are eligible, provided they have no evidence of acute or chronic Graft-versus-Host Disease (GVHD), are not receiving GVHD prophylaxis or treatment, and are at least 90 days post-transplant at the time of enrollment.

D. Hematopoietic growth factors: It must have been at least 7 days since the completion of therapy with G-CSF or other growth factors at the time of enrollment. It must have been at least 14 days since the completion of therapy with long-acting filgrastim (pegfilgrastim or biosimilar)

E. Biologic (anti-neoplastic agent):

At least 7 days since the last dose of a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair

- **Monoclonal antibodies**: At least 3 half-lives of the antibody or 21 days (whichever is shorter) must have elapsed after the last dose of monoclonal antibody. (i.e., blinatumomab half-life = 6 hours,[44] therefore wash-out is 18 hours; inotuzumab half-life = 37 days therefore wash-out is 21 days; rituximab half-life = 66 days, therefore wash-out is 21 days). If steroids are being used to modify immune-related adverse events of antibody therapy, at least 14 days must have elapsed since the last dose of corticosteroid.

- **Immunotherapy**: At least 30 days after the completion of any type of immunotherapy, e.g., tumor vaccines, CAR T cells. If steroids are being used to modify immune-related adverse events of immunotherapy, at least 14 days must have elapsed since the last dose of corticosteroid.

F. XRT: Craniospinal XRT is prohibited during protocol therapy. No washout period is necessary for radiation given to any extramedullary site other than CNS; ≥90 days must have elapsed if prior total body irradiation (TBI) or craniospinal XRT.

G. Anthracyclines: Patients must have had a lifetime exposure of <400 mg/m^2 of doxorubicin equivalents of anthracyclines (anthracycline equivalence to doxorubicin conversion, see Appendix IV).

H. Proteasome inhibitors: Patients with a prior exposure to proteasome inhibitors (e.g., bortezomib, carfilzomib) are eligible as long as the patient demonstrated at least a partial response (see Section 11) to a proteasome inhibitor with chemotherapy combination. This criteria only applies to the Phase 2 portion of the study.

3.3.5 Renal and hepatic function

Patients must have adequate renal and hepatic functions as indicated by the following laboratory values:

A. Adequate renal function defined as: Patient must have a calculated creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73m^2 OR a normal serum creatinine based on age/gender in the chart below:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

B. Adequate Liver Function Defined as: Direct bilirubin ≤ 1.5 x upper limit of normal (ULN) for age or normal (except in the presence of Gilbert's syndrome), AND alanine transaminase (ALT) ≤ 5 x ULN for age. The hepatic requirements are waived for patients with known or suspected liver involvement by leukemia or lymphoma. This must be reviewed by and approved by the study chair or vice chair.

3.3.6 Adequate Cardiac Function Defined as**:** Shortening fraction of ≥ 27% by echocardiogram, OR ejection fraction of ≥ 50% by radionuclide angiogram (MUGA).

3.3.7 Reproductive Function

A. Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed within 2 weeks prior to enrollment.

B. Female patients with infants must agree not to breastfeed their infants while on this study.

C. Male and female patients of child-bearing potential must agree to use an effective method of contraception approved by the investigator during the study and for a minimum of 6 months after study treatment.

3.3.8 Informed Consent

Patients and/or their parents or legal guardians must be capable of understanding the investigational nature, potential risks and benefits of the study. All patients and/or their parents or legal guardians must sign a written informed consent. Age appropriate assent will be obtained per institutional guidelines. To allow non-English speaking patients to participate in this study, bilingual health services will be provided in the appropriate language when feasible.

3.3.9 Protocol Approval

All institutional, FDA, and OHRP requirements for human studies must be met.

3.4 Exclusion Eligibility Criteria

Patients will be excluded if they meet any of the following criteria

3.4.1 Patients will be excluded if they have isolated CNS or testicular disease.

3.4.2 Patients will be excluded if they have ≥ grade 2 peripheral sensory or motor neuropathy (defined by the Modified "Balis" Pediatric Scale of Pediatric Neuropathies) at the time of enrollment (see section 4.7.1.1).

3.4.3 Patients will be excluded if they have a known allergy or intolerance to any of the drugs used in the study – except for Pegaspargase or Calaspargase for which asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) or (if available) crisantaspase (Erwinase®), may be substituted for allergy to Pegaspargase or Calaspargase

3.4.4 Patients will be excluded if they have a systemic fungal, bacterial, viral or other infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The patient needs to be off pressors and have negative blood cultures for 48 hours.

3.4.5 Patients will be excluded if there is a plan to administer non-protocol chemotherapy, radiation therapy, or immunotherapy during the study period.

3.4.6 Patients will be excluded if they have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with the protocol treatment or procedures, interfere with consent, study participation, follow up, or interpretation of study results.

3.4.7 Patients with DNA fragility syndromes (such as Fanconi anemia, Bloom syndrome) are excluded.

3.4.8 Patients will be excluded if they have had a lifetime exposure of ≥400 mg/m^2 doxorubicin equivalents of anthracyclines (anthracycline equivalence to doxorubicin conversion, see Appendix IV).

3.4.9 Concomitant medications

3.4.9.1 Investigational drugs: Patients currently receiving another investigational drug are not eligible.

3.4.9.2 Anti-GVHD agents post-transplant: patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post hematopoietic stem cell transplant are not eligible.

3.4.9.3 CYP3A4 agents: patients who are currently receiving drugs that are strong inducers of CYP3A4 are not eligible. See Appendix II for a list of agents which fall into this category.

3.4.10 Patients with Ph+ALL and Ph-like ALL who are currently receiving TKI therapy

4.0 TREATMENT PROGRAM

The following sections detail the treatment plan for each block of therapy. Please refer to the Drug Information section for additional administration guidelines. Treatment should begin within 3 calendar days following enrollment.

Phase 1 – PO For ixazomib dose escalation details see section 4.5. Patient will receive the same dose in block 1, block 2, and optional maintenance therapy.

Phase 2 – Both phase 1 and 2 will use the same treatment program.

Timing of protocol therapy administration, toxicity and response assessments, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. With the exception of the start date, minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except when explicitly prohibited within the protocol).

4.1 Block 1 (35 days)

Use treatment dose based on age on day of administration. For ixazomib, dose should be based on Day 1 BSA/weight (- 3 days) and remain consistent throughout a cycle unless the patient's BSA changes by more than 10% at which point the dose should be adjusted to meet the new BSA

Please see Section 4.7 for ixazomib dose modifications for ixazomib-related toxicities.

- DLT will be assessed during block 1 only (Refer to Section 4.6).

Days	1	2	4	8	9	11	14	15	16	18	22	23	29	30
Ixazomib**	●		●	●		●							BM	
Vincristine IV (1.5mg/m^2)	●			●				●			●			
Dexamethasone IV/PO (10mg/m^2)	→	→	→	→	→	→	→							
Pegaspargase IV/IM (2500 IU/m^2)√ ±		●						●						
OR Calaspargase IV (2500 IU/m^2) √ ±		●												
Doxorubicin (60mg/m^2)	●													
Initial IT chemotherapy*	●													
CNS 1/2: IT Methotrexate								●					●‡	
CNS 3: ITT#				●				●			●		●‡	
Leucovorin IV/PO (5 mg/m^2 at hr 24 and 30 post-ITs^		●			●				●			●		●

Dose for patient < 1 years of age see below
IT – intrathecal therapy; ITT – Triple IT
√ Either Pegaspargase OR Calaspargase will be administered according to current approved labeling based on age and regional availability. Patients who start on either Pegaspargase or Calaspargase must continue the same treatment throughout the treatment cycle and are not to be used interchangeably. Patients receiving Calaspargase will only receive one dose in this cycle
± asparaginase Erwinia chrysanthemi (recombinant)-rywn Rylaze ®)OR crisantapase (Erwinase®) may be substituted for allergy to Pegaspargase OR Calaspargase. If reaction to Day 2 calaspargase requires Erwinia replacement, 2 courses of Erwinia (beginning at or around Day 2 and at or around Day 15) should be administered (i.e. 12 total Erwinia doses). See below.
* Initial IT – age based dosing. May include MTX, ITT, or cytarabine. Patient may receive up to 7 days prior to initiation of the systemic chemotherapy.
# ITT therapy for infants is described in detail below.
‡ IT therapy assigned to be given on Day 29 may be moved such that it may be given at the time of the end of Block 1 bone marrow/disease evaluation.
^For patients with DS only (based on dates when IT MTX or ITT given)

****Timing of ixazomib**

- After administration of vincristine, doxorubicin, and IT (if applicable)

Ixazomib

Days 1, 4, 8, and 11. Note: at least 72 hours must have elapsed between doses

Dose Phase 1 – Assigned upon study entry.
Phase 2 – PO formulation at RP2D (2 mg/m^2 for non-DS patients) Down syndrome patients will receive 1.6 mg/m^2

Vincristine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 8, 15 and 22

Dose: ≥ 1 year: 1.5mg/m^2/dose (maximum dose 2mg)
≥ 6 months and < 1 year: 1.2mg/m^2/dose
< 6 months: 1mg/m^2/dose

Dexamethasone: PO or IV

Days 1-14

Dose: ≥ 1 year: 10mg/m^2/day, divided BID (i.e., 5mg/m^2/dose, BID)
≥ 6 months and < 1 year: 8mg/m^2/day, divided BID (i.e., 4 mg/m^2/dose, BID)
< 6 months: 7mg/m^2/day, divided BID (i.e., 3.5 mg/m^2/dose, BID)

Pegaspargase: IV over 1-2 hours or IM

Days 2, 15

Dose ≥ 1 year: 2,500 International units (IU)/m^2/dose
≥ 6 months and < 1 year: 2,000 IU/m^2/dose
< 6 months: 1,750 IU/m^2/dose

OR

Calaspargase: IV over 1-2 hours

Day 2

Dose ≥ 1 month and < 22 years of age: 2,500 International units (IU)/m^2/dose

Due to the pharmacokinetics and pharmacodynamics of Calaspargase, the half-life of Calaspargase asparagine depletion was significantly longer than that of Pegaspargase at conventional dosing (2500 IU/m^2)[58,59] therefore patients receiving Calaspargase will only receive one dose in this cycle.
If reaction to calaspargase requires Erwinia replacement, 2 courses of Erwinia (beginning at or around Day 2 and at or around Day 15) should be administered (i.e. 12 total Erwinia doses). See below.

NOTE: Obesity (defined as ≥ 95% BMI for age for patients < 20 y.o or BMI ≥30 for patients ≥ 20 y.o) has been linked to increased risk of toxicity in patients ≥ 10 years of age.

- Dose capping at 3,750 units/dose (1 vial) per institutional policy is permissible in cases of baseline obesity.

For severe allergic reaction, discontinue pegaspargase or calaspargase and substitute asparaginase Erwinia therapy. Asparaginase Erwinia therapy should begin within 72 hours of the pegaspargase or calaspargase reaction or sooner if possible. Either of the following asparaginase Erwinia formulations are permissible if available: asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze) or crisantaspase (Erwinase), Refer to prescribing information for dosing of asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) or crisantapase (Erwinase®) . Please note that the most current FDA approved dosing route and schedule of Rylaze® or Erwinase® should be followed at the time of administration. If available and approved Crisantaspase (Erwinase®) should be dosed at the FDA

approved dose of asparaginase 25,000 International Units/m^2. .The number of doses of Erwinia should be based on pegaspargase replacement. That is: if a reaction to the Day 2 pegaspargase requires Erwinia repalacement, 12 total doses of Erwinia will be administered (6 dose for the Day 2 dose of pegaspargase and 6 doses for the Day 15 dose). If there is a reaction to the Day 15 pegaspargase which requires Erwinia replacement 6 doses will be administered. If reaction to calaspargase requires Erwinia replacement, 2 courses of Erwinia (beginning at or around Day 2 and at or around Day 15) should be administered (i.e. 12 total Erwinia doses).
Route of administration, dose schedule and total doses administered should be documented, as this could contribute to variability in PK data for ixazomib.

Dosing guideline for crisantapase (Erwinase®):
≥ 1 year: 25,000 IU/m^2/dose
≥ 6 months and < 1 year: 20,000 IU/m^2/dose
< 6 months: 17,500 IU/m^2/dose

Dosing guideline for asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®):
Refer to current FDA product information for dosing Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) at the time of product administration.

Doxorubicin: IV over 15 minutes
Day 1
Dose ≥ 1 year: 60 mg/m^2/dose
≥ 6 months and < 1 year: 48 mg/m^2/dose
< 6 months: 42 mg/m^2/dose

Initial IT chemotherapy:
Day 1, age-based dosing (see below). May include MTX, Triple IT, or cytarabine.

IT Methotrexate: for CNS 1/2 patients only
Days IT methotrexate given intrathecally to patients on days 15 and 29‡.
Omit IT methotrexate on Day 1 of course 1 if patient received IT therapy within 7 days prior to study enrollment as part of diagnostic lumbar puncture procedure.
‡IT therapy assigned to be given on Day 29 may be moved such that it may be given at the time of the end of Block 1 bone marrow/disease evaluation.

Dose Defined by age (yrs.)
- 6 mg patients age < 1
- 8 mg for patients age 1-1.99
- 10 mg for patients age 2-2.99
- 12 mg for patients 3-8.99 years of age
- 15 mg for patients ≥9 years of age

Triple IT: for CNS 3 patients only
Days 8, 15, 22, and 29‡
Dose Defined by age (yrs.)

Age (yrs.):	Dose Methotrexate (MTX)	Hydrocortisone (HC)	Cytarabine (ARAC)
< 1 years	MTX: 6mg	HC: 12 mg	ARAC: 15 mg
1 – 1.99	MTX: 8 mg,	HC: 8 mg,	ARAC: 16 mg
2 – 2.99	MTX: 10 mg,	HC: 10 mg,	ARAC: 20 mg
3 – 8.99	MTX: 12 mg,	HC: 12 mg,	ARAC: 24 mg
≥ 9	MTX: 15 mg,	HC: 15 mg,	ARAC: 30 mg

‡IT therapy assigned to be given on Day 29 may be moved such that it may be given at the time of the end of Block 1 bone marrow/disease evaluation.

Leucovorin: PO or IV FOR DOWN SYNDROME PATIENTS ONLY
Days 2, 9, 16, 23, 30 (based on dates when IT MTX or ITT given)
Dose: 5 mg/m^2/dose x 2 doses given 24 and 30 hours after IT methotrexate or ITT

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

IT Cytarabine (for initial IT chemotherapy)
Days 1 (may be administered up to 7 days prior to the initiation of systemic chemotherapy)
Dose Defined by age (yrs.)
- 15mg for patients < 1
- 30mg for patients age 1-1.99
- 50mg for patients age 2-2.99
- 70mg for patients age ≥ 3

4.2 Block 2 (35 days)

4.2.1 Criteria to begin block 2 therapy

- If patients achieve CR/CR MRD-/CRi after block 1, they will have the option of continuing with block 2 therapy, moving directly on to the maintenance cycle for up to 4 cycles, or going off protocol therapy. If patients have PR/SD, they will continue with block 2 therapy. After completion of block 2 therapy, subjects with CR/CR MRD-/CRi/PR can participate in an optional maintenance cycle for up to 4 cycles.
- Block 2 therapy should start as soon as all grade 3 and 4 non-hematologic toxicities have resolved to grade 2 or less, and patient is clinically acceptable to receive therapy judged by treating physician.
- **Please start dexamethasone and vincristine if the count has not yet recovered (ANC ≥ 500/µL and platelet ≥ 20,000/µL, platelet infusion independent) but patient is well and the bone marrow evaluation has been performed and CR/CR MRD-/CRi/PR/SD is confirmed (see section 4.3)**
- Patients with progression of disease (PD) will be removed from study (response criteria see 11.0).

4.2.2 **Block 2**

Therapy delivery map
Please see Section 4.7 for ixazomib dose modifications for ixazomib-related toxicities.

Days	1	3	4	5	8	9	10	11	15	18	19	21
Ixazomib**	●		●		●				●	●		

Dexamethasone IV/PO (6mg/m^2)	→	→	→	→								
Vincristine IV (1.5mg/m^2)		●										
Methotrexate IV (1000mg/m^2)*					●							
Pegaspargase IV/IM (2500 IU/m^2) √ ±						●						
OR Calaspargase IV (2500 IU/m^2) √ ±						●						
Cyclophosphamide IV (440mg/m^2)#									→	→	→	
Etoposide IV (100mg/m^2)#									→	→	→	
CNS 1/2: IT Methotrexate					●							
CNS 3: ITT					●$							
Leucovorin IV/PO (15 mg/m^2)							●	→				

Dose for patient < 1 years of age see below

***Timing of Day 8 therapy**

- For patients beginning block 2 with M1 marrow, proceed to day 8 chemotherapy only when ANC ≥ 500/µL and platelet ≥ 20,000/µL, platelet infusion independent.
- Patients beginning block 2 with M2/M3 marrow should proceed without count recovery

#Timing of Day 15 therapy

- Await count recovery to ANC ≥ 500/µL and platelet ≥ 20,000/µL, platelet infusion independent, prior to beginning day 15 chemotherapy

****Timing of Ixazomib**

- Day 8: after IT methotrexate, before IV methotrexate
- Day 15, 18: after administration of cyclophosphamide and etoposide

√ Either Pegaspargase OR Calaspargase will be administered according to current approved labeling based on age and reasonable availability. Patients who start on either Pegaspargase or Calaspargase must continue the same treatment throughout the treatment cycle and are not to be used interchangeably.

± crisantapase (Erwinase®) or asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) may be substituted for allergy to Pegaspargase or Calaspargase. See below.

$Dose of IT therapy for infants: IT methotrexate and hydrocortisone as listed below

Ixazomib

Days 1, 4, 8, 15, and 18. Note: at least 72 hours must have elapsed between doses

Dose Phase 1 – Assigned upon study entry. Dose will not change during the treatment in the same patient
Phase 2 – PO formulation at RP2D (2 mg/m^2 for non-DS patients) Down syndrome patients will receive 1.6 mg/m^2

Dexamethasone: PO or IV

Days 1-5

Dose ≥ 1 year: 6mg/m^2/day, divided BID (i.e., 3mg/m^2/dose, BID)
≥ 6 months and < 1 year: 5 mg/m^2/day, divided BID (i.e., 2.5 mg/m^2/dose, BID)
< 6 months: 4 mg/m^2/day, divided BID (i.e., 2 mg/m^2/dose, BID)

Vincristine: IV push over 1 minute or infusion via minibag as per institutional policy

Day 3

Dose ≥ 1 year: 1.5mg/m^2/dose (maximum dose 2mg)

≥ 6 months and < 1 year: 1.2mg/m^2/dose
< 6 months: 1mg/m^2/dose

Intermediate-dose Methotrexate: IV over 36 hours. Timing of methotrexate see above.
Day 8
Does ≥ 1 year: 1,000 mg/m^2/dose, given as a 100mg/m^2 bolus over 30 min followed by 900mg/m^2 over 35.5 hrs.
≥ 6 months and < 1 year: 800 mg/m^2/dose, given as a 80mg/m^2 bolus over 30 min followed by 720mg/m^2 over 35.5 hrs.
< 6 months: 700 mg/m^2/dose, given as a 70mg/m^2 bolus over 30 min followed by 630mg/m^2 over 35.5 hrs.
Be certain that the MTX infusion is completed in the 36 hour period

Suggested hydration and alkalinization: Start hydration at least 6 hours prior to the start of methotrexate. Hydrate with D5¼NS with 30mEq NaHCO3/L at 125 ml/m^2/hr to achieve a urine specific gravity ≤ 1.010 and pH between 7 and 8. Ringers lactate maybe used as initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 min) may be given to raise the urine pH relatively quickly. A normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout MTX infusion after its completion until the last dose of Leucovorin has been given.

Leucovorin: PO/IV
Days 10, 11
Dose (for non-DS patients)15mg/m^2/dose every 6 hours beginning 48 hours after the START of methotrexate infusion.
- If 48 hour methotrexate level is ≤ 0.5μM, do not give more than two doses of leucovorin (48 and 54 hours)
- If methotrexate level at 48 hours is > 0.5μM, then continue hydration and leucovorin rescue at 15mg/m^2/dose PO/IV every 6 hours until methotrexate level is < 0.1μM

(for DS patients) Dose: 15mg/m^2/dose every 6 hours beginning 42 hours after the START of methotrexate infusion and continue for a minimum of 5 doses (Hr 42, 48, 54, 60 and 66) if 48 hour plasma methotrexate level is ≤ 0.2 μM may stop after hour 66 dose.

- If methotrexate level at 48 hour is > 0.2μM, then continue hydration and leucovorin rescue at 15mg/m^2/dose PO/IV every 6 hours until methotrexate level is < 0.1μM

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Hold trimethoprim/sulfamethoxazole (TMP-SMX), any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of ID MTX infusion and for at least 72 hours after the start of the ID MTX infusion and until the MTX level is less than 0.5 μM for ID MTX.

Pegaspargase: IV over 1-2 hours (or IM) Day 9 or 10, administer 4 hours after completion of day 8 IV methotrexate
Dose ≥ 1 year: 2,500 International units (IU)/m^2/dose
≥ 6 months and < 1 year: 2,000 IU/m^2/dose
< 6 months: 1,750 IU/m^2/dose

OR

Calaspargase: IV over 1-2 hours
Day 9 or 10, administer 4 hours after completion of day 8 IV methotrexate

Dose ≥ 1 month and < 22 years of age: 2,500 International units (IU)/m^2/dose

NOTE: Obesity (defined as ≥ 95% BMI for age for patients < 20 y.o or BMI ≥30 for patients ≥ 20 y.o) has been linked to increased risk of toxicity in patients ≥ 10 years of age.

- Dose capping at 3,750 units/dose (1 vial) per institutional policy is permissible in cases of baseline obesity.

For patients with severe allergic reaction to pegaspargase or calaspargase may substitute asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze).or crisantaspase (Erwinase), Refer to prescribing information for dosing of asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) or crisantapase (Erwinase®) . Please note that the most current FDA approved dosing route and schedule of Rylaze® or Erwinase®should be followed at the time of administration. If available and approved Crisantaspase (Erwinase®) should be dosed at the FDA approved dose of asparaginase 25,000 International Units/m^2 administered IM or IV over 1-2 hours three times a week (Monday/Wednesday/Friday) for six doses for each dose of planned pegaspargase. Six doses of replacement Erwinia should be given to replace either pegaspargase or calaspargase during Block 2.

Route of administration, dose schedule and total doses administered should be documented, as this could contribute to variability in PK data for ixazomib

Dosing guideline for crisantapase (Erwinase®):
≥ 1 year: 25,000 IU/m^2/dose
≥ 6 months and < 1 year: 20,000 IU/m^2/dose
< 6 months: 17,500 IU/m^2/dose

Dosing guideline for asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®):
Refer to current FDA product information for dosing Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) at the time of product administration.

Cyclophosphamide: IV over 15-30 minutes. Timing of Cyclophosphamide see above
Days 15-19
Dose ≥ 1 year: 440 mg/m^2/dose
≥ 6 months and < 1 year: 350 mg/m^2/dose
< 6 months: 300 mg/m^2/dose

Etoposide: IV over 1-2 hours. Timing of Etoposide see above
Days 15-19
Dose ≥ 1 year: 100 mg/m^2/dose
≥ 6 months and < 1 year: 80 mg/m^2/dose
< 6 months: 70 mg/m^2/dose

IT Methotrexate: for CNS1/2 patients only
Day 8
Dose Defined by age
– 6 mg patients age < 1
– 8 mg for patients age 1-1.99

- 10 mg for patients age 2-2.99
- 12 mg for patients 3-8.99 years of age
- 15 mg for patients ≥9 years of age

Triple IT: for CNS 3 patients only

Day 8
Dose Defined by age

Age (yrs.):	Dose Methotrexate (MTX)	Hydrocortisone (HC)	Cytarabine (ARAC)
< 1	MTX: 6 mg	HC: 12 mg	ARAC: 15 mg
1 – 1.99	MTX: 8 mg,	HC: 8 mg,	ARAC: 16 mg
2 – 2.99	MTX: 10 mg,	HC: 10 mg,	ARAC: 20 mg
3 – 8.99	MTX: 12 mg,	HC: 12 mg,	ARAC: 24 mg
≥ 9	MTX: 15 mg,	HC: 15 mg,	ARAC: 30 mg

Leucovorin: PO or IV FOR DOWN SYNDROME PATIENTS ONLY
Day 9 (based on dates when IT MTX or ITT given)
Dose: 5 mg/m^2/dose x 2 doses given 24 and 30 hours after IT methotrexate or ITT

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

4.3 Optional standard maintenance cycle

4.3.1 Criteria to begin maintenance therapy

- If patients achieve CR/CR MRD-/CRi after block 1, they will have the option of moving directly on to the maintenance cycle for up to 4 cycles. After completion of block 2 therapy, subjects with CR/CR MRD-/CRi/PR can also participate in the optional maintenance cycle for up to 4 cycles[$].
- Block 2 therapy should start when patient is clinically acceptable to receive therapy judged by treating physician

4.3.2 Therapy Delivery Map

Please see Section 4.7 for ixazomib dose modifications for ixazomib-related toxicities.

Days	1	2	5	8	11	15	18	22	28
Ixazomib[$]	●			●		●			
Vincristine IV (1.5mg/m^2)	●								
Prednisone (20mg/m^2/dose BID)	→	→	→						
Mercaptopurine (75mg/m^2/day)[#]	→	→	→	→	→	→	→	→	→
Methotrexate 20mg/m^2/week*	●			●		●		●	
IT Methotrexate[#]	●								

Leucovorin IV/PO (5 mg/m^2 at hr 24 and 30 post-IT)**		•							

Dose for patient < 1 years of age see below

$ Patients on maintenance cycle can receive compassionate use of ixazomib with maintenance chemotherapy for up to 12 months.
# Standard dose for mercaptopurine is 75mg/m2/day. The dose can be modified by treating physician based on TPMT and/or NUDT15 genotype and based on platelet/ANC (see dose modification sections).
* Oral methotrexate dose will be omitted in the week of IT methotrexate dosing
# Optional per treating physician
** For patients with DS only

****Timing of ixazomib administration**

- After administration of vincristine and IT (if applicable)

Ixazomib
Days 1, 8, and 15
Dose We will use PO formulation at RP2D
Phase 1 – Assigned upon study entry. Dose will not change during the treatment in the same patient
Phase 2 – PO formulation at RP2D (2 mg/m^2 for non-DS patients) Down syndrome patients will receive 1.6 mg/m^2

Vincristine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1
Dose ≥ 1 year: 1.5mg/m^2/dose (maximum dose 2mg)
≥ 6 months and < 1 year: 1.2mg/m^2/dose
< 6 months: 1mg/m^2/dose

Prednisone
Days 1-5
Dose ≥ 1 year: 40mg/m^2/day, divided BID (i.e., 20mg/m^2/dose, BID)
≥ 6 months and < 1 year: 32 mg/m^2/day, divided BID (i.e., 16 mg/m^2/dose, BID)

Mercaptopurine: PO
Days 1-28
Dose ≥ 1 year: 75mg/m^2/day, QHS
≥ 6 months and < 1 year: 56mg/m^2/day, QHS

Methotrexate: PO
Day 1, 8, 15, 22, hold on the week of receiving LP/IT
Does ≥ 1 year: 20mg/m2/dose
≥ 6 months and < 1 year: 15mg/m2/dose

IT Methotrexate: optional
Day 1
Dose Defined by age
– 6 mg patients age < 1
– 8 mg for patients age 1-1.99
– 10 mg for patients age 2-2.99
– 12 mg for patients 3-8.99 years of age

– 15 mg for patients ≥9 years of age

Triple IT: optional for CNS 3 patients only

Day 1
Dose Defined by age

Age (yrs.):	Dose Methotrexate (MTX)	Hydrocortisone (HC)	Cytarabine (ARAC)
< 1	MTX: 6 mg	HC: 12 mg	ARAC: 15 mg
1 – 1.99	MTX: 8 mg,	HC: 8 mg,	ARAC: 16 mg
2 – 2.99	MTX: 10 mg,	HC: 10 mg,	ARAC: 20 mg
3 – 8.99	MTX: 12 mg,	HC: 12 mg,	ARAC: 24 mg
≥ 9	MTX: 15 mg,	HC: 15 mg,	ARAC: 30 mg

Leucovorin: PO or IV FOR DOWN SYNDROME PATIENTS ONLY
Days 2 (based on dates when IT MTX or ITT given)
Dose: 5 mg/m2/dose x 2 doses given 24 and 30 hours after IT methotrexate or ITT

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

4.4 Disease Evaluation

4.4.1 Disease evaluation end block 1

- A bone marrow aspiration (biopsy is optional) and CT and PET (lymphoma patients only) to assess remission status should be performed no earlier than day 29. For lymphoma patients, Gallium scan may be substituted for PET scan at sites where PET is not available. PET without CT should not be used as a substitute for CT with contrast. Combined PET/CT is acceptable.
- The bone marrow evaluation may be delayed no later than day 36 (± 1 day) if ANC < 500/µL and platelet < 20,000/µL, platelet infusion independent, on day 29.
- If the marrow is hypoplastic and/or there is little or no evidence of normal hematopoiesis, a repeat marrow should be performed after every 7-21 days (based upon peripheral blood count recovery and the clinician's judgment) and remission status assessed at this later time point.
- For lymphoma patients, if the bone marrow was M1 marrow with negative MRD at the beginning of the block 1, repeat bone marrow aspiration/biopsy is not necessary.

4.4.2 Disease evaluation end block 2 (only applies to leukemia patients not in MRD negative CR, or lymphoma patients not in CR)

- A bone marrow aspiration (biopsy is optional) and CT and PET (lymphoma patients only) to assess remission status should be performed no earlier than day 29 (± 3 days). Gallium scan may be substituted for PET scan at sites where PET is not available. PET without CT should not be used as a substitute for CT with contrast. Combined PET/CT is acceptable.
- The evaluation may be delayed no later than day 36 (± 1 day) if ANC < 500/µL and platelet < 20,000/µL, platelet infusion independent, on day 29.

4.5 Dose Escalation Schedule

Phase 1 (PO formulation): The following dose levels for ixazomib are planned starting at dose level 1

Level	Patients ≥ 1 year of age Dose	Patients < 1 year of age Dose
-1	1.2 mg/m^2/day	0.04 mg/kg/day
1	1.6 mg/m^2/day	0.05 mg/kg/day
2	2 mg/m^2/day	0.07 mg/kg/day

4.6 Dose-limiting Toxicity (DLT)

Toxicity will be graded according to the NCI Common Toxicity Criteria (CTC) version 5.0. A copy of the CTCAE can be downloaded from the CTEP home page: (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf#search=%22CTCAE%22). Any DLT should be reported immediately through the TACL Operation Center to the Study Chair.

For the purposes of determining DLT/dose escalation: DLT will be assessed in the first block only and only in non-DS children ≥ 1 year of age. Since infants and patients with DS have more toxicities with chemotherapy, the toxicity data of those patients will be collected but will not be used as DLT assessment.

DLT will be defined as any of the following events that are deemed by the investigator as **possibly, probably, or definitely** attributable to ixazomib:

1) Any Grade 4 non-hematologic toxicity that occurs after the first dose of ixazomib, and is **probably or definitely** attributable to ixazomib, with the following **exceptions**:
   (a) Fever or infection with or without hospitalization
   (b) Fatigue and gastrointestinal symptoms (anorexia, vomiting, dehydration, mucositis)
   (c) Hypofibrinogenemia
   (d) Metabolic/laboratory abnormalities that resolve to ≤ Grade 2, either
      i. prior to the start of the next block of chemotherapy, or
      ii. within 7 days

2) Any Grade 4 non-hematologic toxicity that occurs after the first dose of Ixazomib that is **possibly** attributable to Ixazomib, and results in omission of the subsequent block of chemotherapy or delay of the beginning of the subsequent block of chemotherapy for greater than 7 days, with the exception of fever or infection.

3) Any Grade 3 non-hematologic toxicity that occurs after the first dose of ixazomib that is **possibly, probably or definitely** attributable to ixazomib, and results in omission of the subsequent block of chemotherapy or delay of the beginning of the subsequent block of chemotherapy for greater than 7 days, with the exception of fever or infection.

4) Hematologic toxicities: Failure to recover a peripheral ANC ≥ 500/μL and PLT ≥ 20,000/μL, platelet infusion independent, due to documented bone marrow hypoplasia (cellularity < 10-20%) within 49 days of the beginning of systemic chemotherapy without evidence of active disease or active infection by bone marrow aspiration. Subjects with abnormal blood counts (Grade 1 through 4) at baseline due to disease will not be evaluable for hematologic DLT and will be considered not having had hematologic DLT.

No other hematologic grade 3 or 4 adverse events will be considered dose-limiting.

4.7 Dose Modifications for Toxicity

4.7.1 Ixazomib related toxicities

4.7.1.1 Peripheral neuropathy will be closely monitored during each block of treatment and toxicities graded. A complete neurological exam that includes at a minimum assessment of cranial nerve function, deep tendon reflexes of the brachioradialis, patellar and achiles tendons, balance, gait and general sensation should be documented prior to the start of therapy.

Neuropathy grading should be based on the maximum toxicity occurring during the previous block. All dose modifications should be based on the worst preceding toxicity. Since vincristine can also cause peripheral neuropathy, dose modification will be performed as follows:

Modifications for Neuropathy and Neuropathic Pain (modifications should be made at any time during a cycle that neuropathies are noted:

Grade 1 with pain* or Grade 2	Hold ixazomib and vincristine until neuropathy has resolved to Grade 1 or baseline. When symptoms subside, restart ixazomib and vincristine at full dose.
Grade 2 with pain* or Grade 3	Hold ixazomib and vincristine until neuropathy has resolved to < Grade 2. When symptoms subside, restart ixazomib at one dose level below and vincristine at full dose.
Grade 4	Discontinue ixazomib and hold vincristine until neuropathy has resolved to < Grade 2. When symptoms subside, restart vincristine at 50% previous dose and escalated to full dose as tolerated.

*pain uncontrolled by NSAID or narcotics.

Modified ("Balis") Pediatric Scale of Peripheral Neuropathies

Peripheral Motor Neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.
- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.
- Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).

4.7.1.2 Renal impairment

Patients with mild to moderate renal impairment (creatinine clearance ([CrCL] ≥ 30 ml/min) were included in all clinical studies of ixazomib. In the population PK model, CrCL was not identified as a significant covariate. Therefore, no dose adjustment is required for patients with mild or moderate renal impairment.

The PK of ixazomib in adult patients with severe renal impairment (CrCL<30 mL/min, including patients with end-stage renal disease [ESRD] requiring dialysis) was examined in a dedicated clinical study (Study C16015). The geometric least squares mean ratio (90% CI) for unbound AUC for the combined analysis of severe renal impairment and ESRD patients requiring hemodialysis versus normal renal function was 1.38 (0.93-2.04), indicating that unbound exposures of ixazomib were 38% higher in these patients compared with patients with normal renal function. For patients with severe renal impairment (creatinine clearance <30mL/min/1.73m2) that is not a DLT (Section 4.6), reduce ixazomib by 1 dose level. For those patients already at dose level -1, reduce ixazomib dose to 0.8 mg/m2.

4.7.1.3 Hepatic impairment

Adult patients with mild hepatic impairment (total bilirubin ≤ the upper limit of the normal range [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin >1-1.5×ULN and any AST) were included in all clinical studies during ixazomib development. In the population PK model,

bilirubin was not identified as a significant covariate on CL; therefore, no dose adjustment is necessary for patients with mild hepatic impairment.

The PK of ixazomib in adult patients with moderate (total bilirubin >1.5-3×ULN) or severe (total bilirubin >3×ULN) hepatic impairment was assessed in a dedicated clinical study (Study C16018). For the combined analysis of moderate and severe hepatic impairment versus normal hepatic function, the geometric least squares mean ratio (90% CI) for unbound dose-normalized AUC was 1.27 (0.75-2.16), indicating that unbound systemic exposures of ixazomib are 27% higher in these patients compared with patients with normal hepatic function. Reduce ixazomib by 1 dose level for patients with severe hepatic impairment (i.e. total bilirubin >3x ULN for age) that is not a DLT (Section 4.6). For those patients already at dose level -1, reduce ixazomib dose to 0.8 mg/m2.

4.7.1.4 Dose de-escalation for non-heme, non-neurologic adverse events due to ixazomib

Ixazomib will be stopped and not restarted for any Grade 4 toxicity probably or definitely related to ixazomib. Ixazomib will be dose de-escalated one lower Dose Level (Section 4.5) for non-excluded Grade 3 and 4 toxicities that are possibly, probably or definitely related to ixazomib.

4.7.1.4.1 Dose de-escalation within a block

If a patient experiences a Grade 3 or 4 ixazomib-related toxicity that does not require cessation of ixazomib (see above), and once this Grade 3 or 4 toxicity resolves to ≤ Grade 1, ixazomib can be restarted at one lower Dose Level (Section 4.5) for subsequent doses. Missed doses of ixazomib in a block will not be made up. See Section 7.4.1.4.5 if ixazomib is discontinued.

4.7.1.4.2 Dose de-escalation between blocks

The ixazomib dose will be decreased one lower Dose Level (Section 4.5) for qualifying Grade 3 or 4 toxicities (see above) that resolve to ≤ Grade 1 prior to the beginning of the next block. Doses reduced for an adverse event will not be re-escalated, even if there is minimal or no toxicity at the reduced dose.

4.7.1.5 Protocol therapy and dose reductions for ixazomib-related toxicities

Patients with an ixazomib-related severe toxicity will discontinue ixazomib but will remain on protocol therapy.

4.7.2 Asparaginase [pegaspargase (Oncospar®), asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®), or crisantaspase (Erwinase®)]

4.7.2.1 Allergy

- *Local Allergic Reactions (inflammation at injection site, swelling)*: Note: these recommendations only apply when the asparaginase product is administered IM. Continue pegaspargase administration in the presence of Grade 1 allergy as defined by CTCAE v5.0 (transient flushing or rash; drug fever < 38ºC).

- *Systemic Allergic Reactions*: Discontinuation may be considered for severe Grade 2 or higher allergic reactions as defined by CTCAE v5.0.

Note: Premedication with antihistamines to decrease the risk of overt allergy symptoms is strongly discouraged since anti-histamine use may mask the appearance of systemic allergy. Systemic allergy is frequently associated with the presence of asparaginase neutralizing antibodies, which render asparaginase therapy ineffective. In the event of severe systemic or recurrent local allergic reaction, asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) or crisantapase (Erwinase®) should be substituted.

- *Anaphylaxis:* Discontinue pegaspargase if the patient develops Grade 3 anaphylaxis as defined by CTCAE v5.0 (symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; allergy-related edema/angioedema; hypotension). If this occurs, crisantapase (Erwinase®) or asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) should be substituted.

  Please note that the most current FDA approved dosing route and schedule of Rylaze® or Erwinase®should be followed at the time of administration. If available and approved Crisantaspase (Erwinase®) should be dosed at the FDA approved dose of asparaginase 25,000 International Units/m^2 administered IM or IV over 1-2 hours three times a week (Monday/Wednesday/Friday) for six doses for each dose of planned pegaspargase.

  The dose modification guidelines for ALL trials recommend the substitution for replacement of Erwinia asparaginase for pegaspargase utilizing the following schedule:

Phases of Treatment	Drugs	Replacement Schedule for Erwinia asparaginase*
Block 1/Block 2	One or more doses of pegaspargase (2,500 IU/m^2)	Crisantaspase (Erwinase®) 25,000 IU/m^2/dose IM or IV M/W/F x 6 doses for each dose of pegaspargase asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) Refer to most current FDA approved dosing route and schedule.

*If a patient develops a Grade 3 or higher anaphylaxis to Erwinia, discontinue future asparaginase therapy. Consider discontinuation for severe Grade 2 or higher allergic reactions

In the event that a pegaspargase infusion is discontinued for an allergic reaction, regardless of amount received, substitution with *Erwinia* asparaginase should begin within 72hours (or sooner if possible) after pegaspargase has been discontinued and continue for up to 6 doses if using Cristantaspase (Erwinase) or per current FDA approved dose and schedule if using Rylaze®.

Erwinia asparaginase may be administered, as tolerated, to replace the incomplete intravenous pegaspargase dose. Of note, *Erwinia* asparaginase is recommended only for pegaspargase hypersensitivity reactions, and not for pancreatitis, hepatitis, coagulation abnormalities, or other non-hypersensitivity toxicities associated with pegaspargase. To best suit the needs of each individual patient, additional modifications to these recommendations may be made at the discretion of the treating physician.

Centers may elect to discontinue pegaspargase and switch to erwinia asparaginase based upon laboratory evidence of silent inactivation of asparaginase activity in the absence of clinical symptoms of hypersensitivity at their discretion.

For use of Erwinia chrysanthemi (recombinant)-rywn (Rylaze®): refer to current FDA product information for dosing at the time of product administration.

4.7.2.2 Coagulopathy

If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

4.7.2.3 Hyperbilirubinemia

Asparaginase may need to be withheld in patients with an elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity..

Direct Bilirubin	Dose Adjustment
< 3.0 mg/dL	Full dose
3.1-5.0mg/dL	Hold pegaspargase and resume when direct bilirubin is < 2 mg/dL
> 5.0 mg/dL	Hold the dose and administer next scheduled dose if toxicity has resolved.

4.7.2.4 Hyperglycemia

Do not modify dose. Treat hyperglycemia as medically indicated.

4.7.2.5 Hyperlipidemia

Do not modify dose.

4.7.2.6 Ketoacidosis

Hold asparaginase until blood glucose can be regulated with insulin.

4.7.2.7 Pancreatitis

Discontinue asparaginase in the presence of Grade 3 or 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until symptoms and signs subside, and amylase/lipase levels return to normal and then resumed. Grade 3-4 pancreatitis is a contraindication to additional asparaginase administration.

4.7.2.8 Thrombosis

Withhold asparaginase until resolved, and treat with appropriate antithrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing LMWH or antithrombotic therapy.

Do not withhold dose for abnormal laboratory findings without clinical correlate. For significant thrombosis, not line related, consider evaluation for inherited predisposition to thrombosis.

CNS Events (bleed, thrombosis or infarction): Hold asparaginase. Treat with FFP, factors or anticoagulation as appropriate. Resume at full dose when all symptoms have resolved (and evidence of recanalization in case of thrombosis by CT/MRI). Consider evaluation for inherited predisposition to thrombosis.

4.7.3 Cyclophosphamide

4.7.3.1 Hematuria

Omit in the presence of macroscopic hematuria. If there is a history of previous significant hematuria, hydrate before cyclophosphamide until specific gravity is < 1.010 and hydrate at 125 mL/m2/hr for 24 hours after dose. Monitor for adequate urine output as per institution guidelines. Give IV mesna at a total dose that is 60% of the cyclophosphamide dose divided to 3 doses (e.g., if the cyclophosphamide dose is 1000 mg/m^2, the total mesna dose is 600 mg/m^2 or 200 mg/m^2/dose). Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat 4 and 8 hours after the start of cyclophosphamide. This total daily dose of mesna can also be administered as IV continuous infusion. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of cyclophosphamide infusion.

4.7.3.2 Renal Dysfunction

If creatinine clearance or radioisotope GFR is < 10 mL/min/1.73m^2, reduce dose of cyclophosphamide by 50%. Prior to dose adjustment of cyclophosphamide, the creatinine clearance should be repeated with good hydration.

4.7.4 Doxorubicin (Anthracycline)

4.7.4.1 Cardiac Toxicity

Discontinue for clinical or echocardiographic evidence of cardiomyopathy (SF < 27% or EF < 50%) or Grade 3 - 4 left ventricular systolic dysfunction (LVSD) per CTCAE version 5.0.

4.7.4.2 Hyperbilirubinemia

Direct Bilirubin	Dose Adjustment
≤ 3.0 mg/dL	Full dose
3.1-5.0 mg/dL	Administer 50% of calculated dose
5.1-6.0 mg/dL	Administer 25% of calculated dose
> 6.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

4.7.4.3 Extravasation:

In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG guidelines.

Do not make up missed doses.

4.7.5 Etoposide (VP-16)

4.7.5.1 Allergic Reaction

Premedicate with diphenhydramine (1-2 mg/kg slow IV push, maximum dose is 50 mg). If symptoms persist, add hydrocortisone 100-300 mg/m^2. Continue to use premedication before etoposide in future. Also consider substituting an equimolar amount of etoposide phosphate, in the face of significant allergy and/or hypotension. Etoposide phosphate is a water soluble prodrug that does not contain polysorbate 80 and polyethyleneglycol, the solubilizing agent in etoposide that may induce allergic reactions and hypotension. Etoposide phosphate is rapidly converted to etoposide *in vivo* and provides total drug exposure, as represented by AUC (0-infinity) that is statistically indistinguishable from that measured for etoposide at equimolar doses.

4.7.5.2 Hypotension

If diastolic or systolic blood pressure (BP) falls 20 mm Hg during infusion, reduce infusion rate by 50%. Start a simultaneous infusion of NS 10 mL/kg if BP fails to recover or falls further. Stop infusion if BP does not recover, continue NS. If the patient has had any episode of hypotension, prehydrate with 0.9% NaCl at 10 mL/kg/hr for 2 hours prior to any subsequent infusion.

4.7.5.3 Renal Insufficiency

If renal function decreases, adjust etoposide as follows: CrCl 10-50 mL/min/1.73 m^2, decrease dose by 25%; if CrCl < 10 mL/min/1.73 m^2, decrease dose by 50%.

4.7.5.4 Hyperbilirubinemia

If direct bilirubin is > 2 mg/dL, decrease dose by 50%. If direct bilirubin is > 5 mg/dL, hold etoposide.

4.7.6 Intrathecal Methotrexate/Triple Intrathecal Therapy

6-Mercaptopurine (6-MP) Thiopurine Pharmacology Testing and Dosage Mercaptopurine is methylated by thiopurine methyltransferase (TPMT) to an inactive metabolite. Patients with polymorphisms in TPMT resulting in decreased activity are more susceptible to toxicities when given mercaptopurine (i.e., myelosuppression). More recently, germline variants in the gene encoding the nucleoside diphosphate–linked moiety X-type motif 15 (NUDT15) have been reported in approximately 4% of Hispanic/Native American and nearly 10% of East Asian children with ALL; these polymorphisms are strongly associated with mercaptopurine intolerance. There are CLIA certified tests for TPMT genotype and phenotype (genotyping can be performed even after recent RBC transfusions), thiopurine metabolites (MMP and TGN measurements), and for NUDT15 polymorphisms. General comments about TGN metabolite testing: High TGN concentrations: high values should not preclude further increases in mercaptopurine doses if ANC is high and there are no contraindications to dose increases. Likewise, high concentrations of methylated derivatives should not influence dosing in asymptomatic patients without hyperbilirubinemia. When ANC is high despite dose increases, consider non-adherence. Although there are no specific values to use to indicate non-adherence, low concentrations of TGN and methylated derivatives in a sample taken after at least three weeks after continuous dosing may indicate non-adherence."

Suggested starting doses of mercaptopurine for patients with known mutations in TPMT/NUDT15

Mercaptopurine	TPMT or NUDT15 Normal metabolizer	TPMT or NUDT15 Intermediate or Possible intermediate	TPMT or NUDT15 Poor Metabolizer
75mg/m^2/day	Full dose (75mg/m^2/day) and adjust every 2 weeks as clinically indicated	Reduced dose (30-80% of normal starting dose) 22.5-60mg/m^2/day) and adjust every 2-4 weeks as clinically indicated	Reduced dose (10% of normal starting dose) 10mg/m^2/day given 3 days a week and adjust every 4-6 weeks as clinically indicated

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4.7.6.1 Systemic toxicity

The dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Instead, leucovorin may be used at a dose of 5 mg/m2/dose every 6 hours x 2 doses, beginning 24 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC < 0.5 x 10^9/L) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

4.7.6.2 An episode of acute neurotoxicity

Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies. These toxicities are poorly understood and currently it is impossible to predict who will suffer these complications. In addition, there are no data clearly linking the occurrence of an acute neurotoxic event with an increased risk of long-term neurocognitive dysfunction, nor do changes present on MRI at the time of an acute event clearly correlate with or predict outcome.

The following guidelines are offered for consideration following an acute event, but it must be recognized that there are little data to support these approaches or any others. Thus the treating physician must evaluate the patient and, with the family, make the best possible decision with respect to the relative risk and benefit of continued therapy.

Following an acute neurotoxic event, a history and physical exam should guide the differential diagnosis. A neurology consult may be of value and should be considered. Seizures and other transient events may be linked to fever, infection, encephalitis, meningitis, hypertension, electrolyte disturbance, hypoglycemia, trauma, intracranial hemorrhage or thrombosis, narcotic withdrawal, illicit drug use, or other causes in addition to the direct side effects of chemotherapy. Appropriate laboratory studies may include, but are not limited to, blood cultures, a CBC, electrolytes, including glucose, calcium, magnesium and phosphorus, renal and liver function studies and/or an examination of the CSF. Imaging studies may include a CT scan and/or an MRI. The CT is commonly normal, in the absence of stroke, but if calcifications are present, this finding may be indicative of a more severe mineralizing leukoencephalopathy. MRI abnormalities may be pronounced, but transient. Posterior reversible encephalopathy may be present on MRI with extensive diffusion abnormalities, but these do not appear to correlate with subsequent

demyelination or gliosis. Additional studies, including MR angiography and/or venogram should be considered, if clinically indicated (e.g., focal deficits).

Many acute events, seizures or episodes of transient hemiparesis, are temporally related to the administration of intrathecal therapy, commonly 9 to 11 days after the IT administration. For patients who return to their "pre-event" status, without residual deficits of physical or neurologic exam, there are few data to support or guide therapeutic interventions. It is reasonable to hold the next dose of IT therapy, or, substitute IT Ara-C for one dose of IT MTX, or triple IT therapy. It is also reasonable to include leucovorin rescue at a dose of 5 mg/m^2 q 6 hrs x 2 doses beginning 24 hours after the LP. This pattern of rescue was associated with a clear diminution in the incidence of acute neurotoxicity in one case series. There have been questions about potential interference of leucovorin with the efficacy of the IT MTX, but there are little data to support or refute this position. Moreover, the administration 24 hours later would minimize any potential interference. If the event does not recur, resumption of standard therapy should be considered, following one modified or omitted IT dose. In the face of multiply recurrent events, or evidence of progressive encephalopathy, another evaluation is warranted and the treating physician may consider a more prolonged or definitive change in therapy. These decisions are extremely difficult and may hinge on an individual's view of the importance of quality of life versus an increase in the risk of relapse. Since the greatest impact of CNS prophylaxis occurs early in therapy, the timing of these events may also influence clinical decisions. Cranial radiation has been suggested as an alternative to continued IT therapy though much of the literature on long-term neurocognitive dysfunction supports a more deleterious effect from CRT than IT therapy. Cranial radiation is not allowed during protocol therapy.

The use of dextromethorphan (DM) has been suggested as a neuroprotectant, capable of preventing NMDA mediated neurotoxicity without prohibitive toxicity. Low dose therapy has been recommended, in part, based on data suggesting that DM is concentrated in brain relative to serum. However, the literature on the use of DM supports a tight dose response relationship, with the likelihood of sparing an initially unaffected area, following ischemic damage, linked to dose, in both clinical trials and animal models of CNS ischemia. At doses thought to be therapeutic, side effects have included nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. In addition, Hollander et al have raised concerns about the potential deleterious effects of long-term NMDA receptor blockade on memory because hippocampal long-term potentiation is dependent on the activation of the NMDA receptor. Thus in the absence of a clinical trial there are few data to support the addition of DM.

4.7.6.3 Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture

Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based doses** that would be given by LP.

NOTE: Obstruction to CSF flow may be a contraindication to intrathecal and/or intraventricular therapy.

4.7.6.4 Viral, bacterial, or fungal meningitis

Omit until resolved.

4.7.7 Intermediate-Dose Methotrexate (ID MTX, refers to IV *MTX* 1000 mg/m^2 given over 36 hrs) and Leucovorin Rescue

4.7.7.1 ID MTX Infusion Guidelines and dose modifications for toxicity

When IT therapy and ID MTX are scheduled for the same day, it is strongly recommended to deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).

Hold trimethoprim/sulfamethoxazole (TMP-SMX), any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of ID MTX infusion and for at least 72 hours after the start of the ID MTX infusion and until the MTX level is less than 0.5 µM for ID MTX. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 µM.*

Recommended Prehydration: to start at least 6 hours prior to commencement of intravenous methotrexate. **Fluid:** D5 ¼ NS with 30 - 50 mEq NaHCO3/L at 125 mL/m^2/hour. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity ≤ 1.010 and pH between 7 and 8. A bicarbonate bolus (25 mEq/m2 over 15 min) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration.

Hour 0: MTX 100 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 900 mg/m^2 given by continuous IV infusion over 35.5 hours. Be certain that the ID MTX infusion is completed in the 36 hour period. **Note, even if the infusion is not complete at this time point, it must be stopped.**

Recommended Post hydration: Continue hydration using D 5 ¼ NS with 30 – 50 mEq NaHCO3/L at 125 mL/m^2/hour (3 L/m^2/day) throughout IDMTX infusion until the last dose of leucovorin has been given. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 µM.

Leucovorin rescue: 15 mg/m^2 PO/IV at 48 and 54 hrs after the start of the MTX infusion. If 48 hr methotrexate level is ≤ 0.5 µM, then only two doses of leucovorin are administered (at 48 and 54 hours). If MTX level at 48 hours is > 0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 µM.
For DS patients begin leucovorin rescue at hour 42 and continue every 6 hours for a minimum of 5 doses [Hour 42, 48, 54, 60 and 66]

Hour 48: Check plasma methotrexate level at 48 hours after start of the methotrexate infusion. If the level is ≤ 0.5 µM, then do not give more than two doses of leucovorin (48 and 54 hours). If MTX level at 48 hours is > 0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 µM.
DS patients: If hour 48 MTX level ⩽ 0.2 µM may stop after hour 66 dose. If hour 48 MTX level > 0.2 µM continue until MTX levels are < 0.1.

For MTX levels that exceed these expected values modify the rescue regimen as noted below and increase hydration to 200 mL/m^2/hr. Monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly, at any time point (> 100% in 24 hours), assure appropriate urine pH and urine volume as above and consider glucarpidase If urine output fails to continue at

80% of the fluid intake, consider furosemide or acetazolamide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G2) (see below).

48 hr MTX level	Leucovorin Rescue
≤ 0.5 µM	Continue 15 mg/m^2 IV/PO q 6hrs for 2 doses.
0.5 – 1 µM	Increase to 15 mg/m^2 q 6 hrs until MTX level < 0.1 µM (draw q 6-24 hrs).
1 – 5 µM	Increase to 15 mg/m^2 q 3 hrs until MTX level < 0.1 µM (draw q 6-24 hrs).
5 – 10 µM	Increase to 100 mg/m^2 q 6hrs until MTX level < 0.1 µM (draw q 6-24 hrs).
> 10 µM	Increase to 1000 mg/m^2 q 6hrs until MTX level < 0.1 µM (draw q 6-24 hrs). Consider glucarpidase.

4.7.7.2 Nephrotoxicity

Postpone course if pre-treatment (MTX) serum creatinine is > 1.5 x baseline or GFR creatinine clearance < 65 mL/minute/1.73m^2. If there is a rising creatinine (> 100% in 24 hours) or the 48 hour methotrexate level is > 10 µ/L consider using glucarpidase. If renal function does not recover, omit MTX. Do not give ID MTX to a patient with this degree or renal impairment, assuming that prolonged excretion can be managed with glucarpidase.

NOTE: For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G2, Voraxaze™). To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300 – 046 – 774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue will remain on study.

Stop leucovorin 2 hours before administering glucarpidase as it is a competitive substrate and may compete with MTX for glucarpidase binding sites.

Dose of glucarpidase: 50 units/kg administered by intravenous bolus over 5 minutes. Reconstitute each vial with 1 mL sodium chloride 0.9% (do not further dilute). Each vial contains 1,000 units/mL (after reconstitution) and round dose up to vial size. No further dose is required.
Maintaining alkalinization of urine with sodium bicarbonate is essential to maintain urinary pH > 7.
It is essential that patients are NOT co-prescribed the following medicines which reduce MTX excretion: NSAIDS, aspirin, ciprofloxacin, co-trimoxazole, penicillin, probenecid, omeprazole.

Two hours after administration of glucarpidase, leucovorin should be administered at a dose of 250 mg/m^2 every 6 hours by IV bolus (maximum rate: 160 mg/min) for up to 48 hours and then decreased based on plasma MTX concentrations to 15 mg/m^2 intravenously or orally every 6 hours until the plasma MTX concentration is < 0.2 µM.

4.7.7.3 Liver dysfunction

Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to a course of intravenous MTX. Blood samples for ALT should not be drawn following the start of MTX infusions as MTX causes significant short term elevation in ALT levels.

ALT	IV Methotrexate
< 10 X ULN	Continue with therapy as scheduled
10 – 20 X ULN	Continue with therapy as scheduled
10 – 20 X ULN for 2 consecutive cycles	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses
> 20 X ULN	Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20 X ULN for > 2 weeks	Evaluate with AST, Bili, Alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV serologies. Consider liver biopsy before additional therapy given. Notify Study Chair.

***** Please see COG Supportive care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp for TMP/SMX substitutions.

Hold IV MTX for direct hyperbilirubinemia of > 2.0 mg/dL.

4.7.7.4 Mucositis

For Grade 3 - 4 mucositis, withhold IV MTX until resolved.

4.7.7.5 Excess extravasation of fluids into tissues (third spacing)

For Grade 3-4 fluid third-spacing, withhold IV MTX until toxicity has resolved to Grade 2 or less.

4.7.8 Dexamethasone

4.7.8.1 Hypertension

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

4.7.8.2 Hyperglycemia

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

4.7.8.3 Pancreatitis

Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis.

4.7.8.4 Osteonecrosis

Do not modify corticosteroid therapy for osteonecrosis (CTCAE v5.0 term: avascular necrosis) during Block 1.

4.7.8.5 Varicella

Steroids should be held during active infection unless being taken as per protocol therapy guidelines. Do not hold during incubation period following exposure.

4.7.8.6 Severe infection

Do not hold or discontinue steroids during Block 1 without serious consideration, as this is a critical period in the treatment of ALL. Later in therapy, one may consider holding steroid until patient achieves cardiovascular stability, except for “stress doses.”

4.7.8.7 Severe psychosis

Dexamethasone dose may be reduced by 50% for severe psychosis. If symptoms persist, switch to prednisone

4.7.9 Vincristine (VCR)

In this protocol, it may be difficult to determine if peripheral neuropathy in Block 1 is due to VCR or ixazomib. Both agents can cause peripheral neuropathy and there is some overlap in their presentation. Ixazomib is commonly associated with painful sensory peripheral neuropathy. VCR neuropathy, in contrast, is commonly associated with motor or mixed neuropathy, including distal extremity weakness.

4.7.9.1 Severe neuropathic pain (Grade 3 or greater)

Please use “Balis” Scale for grading neuropathy (see text box in 4.7.1.1)

Hold dose(s). When symptoms subside, resume at 50% previous calculated VCR dose (maximum dose: 1 mg), then escalate to full dose as tolerated. NOTE: neuropathic pain can be not only severe but difficult to treat. However, because vincristine is an important component of curative therapy and the majority of neuropathies are ultimately reversible, vincristine therapy may be given at full dose at investigator discretion. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out Charcot Marie Tooth Disease (CMT), Type 1A or Hereditary neuropathy with liability to pressure palsies. Drugs such as gabapentin may be of value.

4.7.9.2 Vocal Cord paralysis

Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. See above for comment on CMT.

4.7.9.3 Foot Drop, paresis

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

4.7.9.4 Jaw pain

Treat with analgesics; do not modify vincristine dose.

4.7.9.5 Hyperbilirubinemia

Direct Bilirubin	Dose Adjustment

⩽ 3.0 mg/dL	Full dose (maximum dose: 2 mg),
3.1- 5.0 mg/dL	50% of calculated dose (maximum dose: 1 mg)
5.1-6.0 mg/dL	75% of calculated dose (maximum dose: 0.5 mg)
> 6.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

4.7.9.6 Constipation or ileus (≥ Grade 3) or typhlitis

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

4.7.9.7 Extravasation

In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG guidelines

5.0 SUPPORTIVE CARE

Best supportive care and treatment will be given as appropriate to each patient (antiemetics, antibiotics, transfusions, oxygen therapy, nutritional support, palliative treatment for pain or cough, etc.). Patients may experience profound myelosuppression and immune suppression during this time. Caregivers must also be made aware that patients may experience very rapid clinical deterioration. This suggests the need for a supportive care network that can recognize and respond to sudden changes in a patient's condition.

Hospitalization during each course of chemotherapy is strongly recommended until the absolute phagocyte count (sum of the neutrophils, bands and monocytes) is rising for two successive days, and the patient is afebrile and clinically stable. An additional discharge criterion of an absolute neutrophil count (ANC) of at least 200/μL is also suggested.

Aggressive supportive care improves outcome. The following guidelines are intended to give general health direction for optimal patient care and to encourage uniformity in the treatment of this patient population. Notify the Study Chair of any unexpected or unusually severe complications.

5.1 Concurrent Therapy

5.1.1 Chemotherapy or Investigational Therapy
Patients must not receive any non-protocol chemotherapy, investigational therapy, or immune modulating agents.

5.1.2 Cranial Irradiation for CNS disease is NOT allowed during protocol therapy.

5.1.3 Radiotherapy for Chloroma is NOT allowed

5.1.4 Appropriate Antibiotics, Blood Products, Antiemetics, Fluids, Electrolytes and general supportive care are to be used as necessary. See section 5.3 for additional information regarding infection control

5.1.5 Patients May Have Received Hydroxyurea to keep WBC below 50,000/µL prior to beginning protocol therapy, but hydroxyurea must be discontinued 24 hours prior to starting systemic protocol therapy.

5.1.6 Cardiac Protectants: Patients can receive cardiac protectants such as Dexrazoxane (Zinecard®) while treated on this protocol per treating physician's decision.

5.1.7 Alternative Medications: Use of alternative medications (eg, herbal or botanical for anticancer purposes) is not permitted during the entire study period.

5.2 Blood Products

Investigators should follow institutional guidelines regarding the administration of blood products.

5.3 Infection Control

5.3.1 Pneumocystis Prophylaxis

All patients are to receive prophylaxis with Trimethoprim/Sulfamethoxazole (TMP-Sulfa) for Pneumocystis for two sequential days each week at a dose of 2.5 mg/kg/dose TMP-Sulfa (maximum dose of 160 mg) twice daily (BID) or according to institutional policy, unless they have a documented sulfa allergy. Sulfa-allergic patients should receive dapsone 2 mg/kg orally (PO) q day with a maximum dose of 100 mg/day, or monthly pentamidine (IV or aerosolized). Pneumocystis prophylaxis should be continued throughout the entire study period.

5.3.2 Bacterial, Fungal and Viral Prophylaxis

Secondary to the high risk of serious invasive bacterial and fungal infection in patients with relapsed ALL and LLy, prophylaxis for bacterial and fungal infections is **MANDATED** on this protocol. Subjects should receive levofloxacin at a dose based on each institution's formulary (but as a recommendation, levofloxacin could be dosed at 10 mg/kg/dose (MAX 750 mg/dose) IV or PO twice daily if <5 years old and at 10 mg/kg/dose (MAX 750 mg/dose) IV or PO once daily if ≥5 years old).

All patients MUST receive antifungal prophylaxis during each course of therapy. Anti-fungal prophylaxis may be given per each institution's standards. It is **strongly encouraged to use a drug with anti-mold activity** such as caspofungin or micafungin. The doses used should be in the treatment range more so than prophylactic as that is when colonization and infection may occur with patients at high risk for fungal infection.

For subjects with a history of documented or suspected HSV or varicella zoster virus infection, it is recommended for them to receive prophylactic acyclovir per institutional standard (as a recommendation acyclovir could be dosed at 750 mg/m^2/day divided BID.)

It is strongly recommended that patients have quantitative immunoglobulins checked per institutional policy, but at least once per cycle. Those with quantitative Ig <500 should receive IVIG monthly.

Bacterial, fungal and viral prophylaxis should be initiated on DAY 8 of each cycle and continued at least until the post-nadir ANC is > 500/µL.

5.3.3 Fever and Neutropenia

All patients with a fever ≥38.5°C on a single occasion, or ≥38°C on 2 occasions within 12 hours, and an ANC <0.50 x 10^9/L are to be hospitalized and treated immediately with intravenous broad-spectrum antibiotics after obtaining appropriate cultures. The specific choice of antibiotics to be used in empiric treatment of febrile neutropenia is dependent on each institution's experience regarding the type of infecting organisms, and their antibiotic sensitivity patterns. Duration of therapy should be determined by site of infection, culture results, and response to treatment. Antifungal treatment is to be considered for the persistence of fever, or emergence of a new fever in neutropenic patients after 3 days of broad-spectrum antibiotic coverage. Surveillance radiographic imaging surveillance for sites of infection should also be performed as clinically indicated. When severe mucositis or a sepsis syndrome is present in patients with febrile neutropenia, or a patient has a history of prior alpha hemolytic sepsis, consider inclusion of Vancomycin in the empiric antibiotic regimen.

5.3.4 Empiric Management of Pulmonary Infiltrates

Pulmonary infiltrates should be evaluated in the context of the patient's clinical and laboratory profile as well as institutional infection patterns. If the patient is not neutropenic, and the pulmonary lesions on CT scan are not particularly suggestive of a fungal infection (Aspergillus, mucor), consider using broad spectrum antibiotics. If the patient develops progressively worsening clinical or laboratory features, or if, the pulmonary lesions on CT scan are suggestive of a fungal infection (Aspergillus, mucor), then more aggressive diagnostic measures should be undertaken. Pulmonary infiltrates may be evaluated with bronchoscopy and biopsy, lavage or open lung biopsy. If a procedure cannot be tolerated, and/or if there is high clinical suspicion consider beginning empiric treatment with amphotericin B given the high likelihood of fungal disease. It is advisable to seek an infectious disease consult under these circumstances. Empiric coverage may include treatment of gram-negative and positive bacteria, Legionella (erythromycin), Pneumocystis (TMP/SMX), and fungi (amphotericin) pending culture results.

If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis are indicated. Surgical excision of pulmonary lesions should be considered at the discretion of the treating physician. Treatment of fungal infections with amphotericin B and/or other antifungal agents will be at the discretion of the treating physician.

5.3.5 Management of Mucositis/Perirectal Cellulitis

Mucositis should be managed with IV hydration and hyperalimentation (if indicated), effective analgesia, broad-spectrum gram-positive and gram-negative antibiotic therapy and empiric antiviral and antifungal therapy as indicated. Management of perirectal cellulitis should include broad-spectrum antibiotic therapy with dual gram-negative coverage as well as anaerobic coverage (i.e. ceftazidime + aminoglycoside + metronidazole; or piperacillin-tazobactam + aminoglycoside), Sitz baths, a strong barrier technique and effective analgesia.

5.3.6 Use of growth factors (G-CSF)

The routine use of G-CSF outside of protocol therapy is not generally recommended, but may be used at the discretion of the investigator in situations such as serious infection with neutropenia.

6.0 DRUG INFORMATION

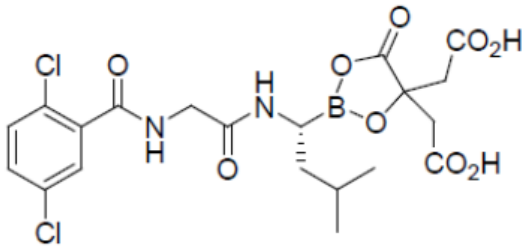
6.1 IXAZOMIB

6.1.1 Nomenclature and Molecular Structure

Ixazomib citrate (Ixazomib citrate (MLN9708), the active pharmaceutical ingredient, is a new active substance and a pro-drug of the active moiety, ixazomib (MLN2238).

The chemical structure of ixazomib citrate (chemical name: CAS: 2,2'-{2-[(1R)-1-({[(2,5-Dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl}diacetic acid; molecular formula: C20H23BCl2N2O9) is presented below.

Figure 1 Chemical structure of ixazomib citrate (MLN 9708)



6.1.2 Mode of Action and Pharmacology

6.1.2.1 Pharmacodynamics related to mechanism of action

In adults, after IV administration, maximum inhibition of 20S proteasome activity occurred within 30 minutes in most patients, indicating rapid target engagement in blood. Prolonged inhibition of 20S proteasome activity (>24 hours) was not apparent. The observed pharmacodynamic profile is consistent with ixazomib being a reversible proteasome inhibitor.

6.1.2.2 Pre-clinical pharmacology data

Pre-clinical safety pharmacology studies and assessments both *in vitro* and *in vivo* indicated that effects on the cardiovascular (CV), respiratory, and nervous system were limited to microscopic neuronal injury, primarily in dogs, that was occasionally associated with neurological clinical signs. The microscopic neuronal injury associated with ixazomib in animals has also been reported with the PI bortezomib and is associated with peripheral neuropathy that has been observed in adult patients treated with bortezomib. Peripheral neuropathy has also been infrequently observed in pediatric patients treated with bortezomib. In adult patients with MM, the reported incidence of peripheral neuropathy after ixazomib treatment was much less than that reported after bortezomib treatment. Ixazomib did not cause the CV electrocardiography effects that have been reported with another PI, carfilzomib.

The overall safety pharmacology data with ixazomib indicate a low potential for CV-, respiratory-, renal, or CNS-related safety pharmacology effects in patients; however, there is a potential for peripheral nervous system effects in both adult and pediatric patients.

Additional details, including results of *in vitro* binding and enzymatic assays, are available in Section 4.2 of the Investigator Brochure

6.1.2.3 Clinical pharmacology data

The clinical pharmacology of ixazomib has been characterized in adults using data from 14 clinical studies. In each study, blood samples (rich or sparse sampling) were collected for assessment of relevant PK endpoints. A population PK analysis has also been performed using data from 755 patients (108 patients receiving IV ixazomib; 647 patients receiving oral ixazomib) enrolled across 10 clinical studies, including the phase 3 study C16010.[45] Two single-agent studies (C16001 and C16002) in 146 patients were conducted with the IV formulation. All other studies have investigated oral ixazomib either alone or in combination with other agents.

The potential for drug-drug interactions with strong CYP3A inhibitors and strong CYP3A inducers and the effect of a high-fat meal on ixazomib PK have been investigated in Study C16009. The ADME properties of ixazomib have been investigated in Study C16016. Studies in special populations have been conducted to investigate the effects of renal impairment (Study C16015)[46] and hepatic impairment (Study C16018)[47] on the PK of ixazomib. Studies have also been conducted in Asian patient populations (Studies C16013 [East Asian patients][48] and TB-MC010034 [Japanese patients]).[49]

The key clinical pharmacology information for ixazomib is summarized below. Please refer to Section 5.3 of the Investigator's Brochure for additional details.

Absorption

After PO administration, ixazomib absorption is fast with an overall median time to maximum observed concentration of approximately 1 hour postdose. The plasma exposure of ixazomib following multiple-dose administration (IV or oral) increased approximately dose proportionally over the 0.48 to 3.95 mg/m^2 dose range (1.4-8.9 mg actual administered dose range) based on noncompartmental analysis. On the basis of the population PK analysis, no readily apparent relationship was observed between the oral dose (0.2-10.6 mg) and apparent oral clearance, supporting the conclusion from the noncompartmental analysis of dose-linear PK. An absolute oral bioavailability of 58% was determined for ixazomib on the basis of the population PK analysis of IV and oral PK data.

The effect of a high-fat meal on the PK of orally administered ixazomib was investigated in adults.[50] A high-fat meal decreased both the rate and extent of ixazomib absorption with a 69% and 28% reduction in the maximum observed concentration (Cmax) and area under the plasma concentration-time curve (AUC), respectively, observed in the fed versus fasted state. The results from this food effect study are consistent with the Biopharmaceutics Classification System Class 3 category of ixazomib.[51] Therefore, PO ixazomib should be taken on an empty stomach, at least 1 hour before or 2 hours after food.

Distribution

The steady-state volume of distribution of ixazomib is large and is estimated to be 543 L on the basis of the population PK model. Ixazomib is 99% bound to plasma proteins and the extent of binding is not altered by severe renal or hepatic impairment. Ixazomib distributes into red blood cells with a blood-to-plasma ratio of 10.

Metabolism

Metabolism is expected to be the major mechanism of clearance (CL) of ixazomib as renal CL contributes approximately 6.4% to total CL. At clinically relevant concentrations of ixazomib, in vitro studies using recombinant CYPs indicated that no specific CYP isozyme predominantly contributes to ixazomib metabolism and that non-CYP proteins contribute to overall metabolism. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor are expected.

Elimination

The geometric mean terminal half-life for ixazomib is 9.5 days and the mean plasma CL is 1.86 L/hr on the basis of the population PK analysis. The geometric mean renal CL of ixazomib is 0.119 L/hr, which is 6.4% of total CL; thereby indicating that renal CL does not meaningfully contribute to ixazomib CL in humans. Taken together with the blood-to-plasma AUC ratio of approximately 10, it can be inferred that ixazomib is a low CL drug.

In the human absorption, distribution, metabolism, and excretion (ADME) study, approximately 62% of the administered radioactive PO dose was recovered in the urine and 22% was recovered in the feces. Only 3.2% of the administered ixazomib dose was recovered in the urine as unchanged drug up to 168 hours after oral dosing, suggesting that most of the total radioactivity in urine was attributable to metabolites. Metabolite profiling of excreta indicated that ixazomib is metabolized to multiple deboronated metabolites that are pharmacologically inactive and predominantly excreted in the urine.

6.1.2.4 Effect of Intrinsic Factors on the PK of Ixazomib

Age, Sex, and Race

There was no clinically meaningful effect of age (23-91 years), sex, or race on the CL of ixazomib on the basis of the results of a population PK analysis. The mean AUC was 35% higher in Asian patients; however, there was overlap in the distribution of AUC across white and Asian patients.

Renal Impairment

Adult patients with mild or moderate renal impairment (creatinine clearance [CrCL] ≥30 mL/min) were included in all clinical studies during ixazomib development. In the population PK model, CrCL was not identified as a significant covariate; therefore, no dose adjustment is required for patients with mild or moderate renal impairment.

The PK of ixazomib in adult patients with severe renal impairment (CrCL<30 mL/min, including patients with end-stage renal disease [ESRD] requiring dialysis) was examined in a dedicated clinical study (Study C16015). The geometric least squares mean ratio (90% CI) for unbound AUC for the combined analysis of severe renal impairment and ESRD patients requiring hemodialysis versus normal renal function was 1.38 (0.93-2.04), indicating that unbound exposures of ixazomib were 38% higher in these patients

compared with patients with normal renal function. A reduced starting dose of ixazomib is recommended for patients with severe renal impairment or ESRD requiring hemodialysis. Ixazomib is not readily dialyzable and thus, can be administered without regard to the timing of dialysis.

Hepatic Impairment

Adult patients with mild hepatic impairment (total bilirubin less than or equal to the upper limit of the normal range [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin >1-1.5×ULN and any AST) were included in all clinical studies during ixazomib development. In the population PK model, bilirubin was not identified as a significant covariate on CL; therefore, no dose adjustment is necessary for patients with mild hepatic impairment.

The PK of ixazomib in adult patients with moderate (total bilirubin >1.5-3×ULN) or severe (total bilirubin >3×ULN) hepatic impairment was assessed in a dedicated clinical study (Study C16018). For the combined analysis of moderate and severe hepatic impairment versus normal hepatic function, the geometric least squares mean ratio (90% CI) for unbound dose-normalized AUC was 1.27 (0.75-2.16), indicating that unbound systemic exposures of ixazomib are 27% higher in these patients compared with patients with normal hepatic function. A reduced starting dose of ixazomib is recommended for patients with moderate or severe hepatic impairment.

Additional details are available in Section 5.3 of the Investigator Brochure.

6.1.3 Drug Interactions

6.1.3.1 CYP Inhibitors

The effect of a strong CYP3A inhibitor on the PK of ixazomib was examined in a dedicated clinical study (C16009 Arm 5). The effect of strong CYP1A2 inhibitors on the PK of ixazomib was examined using population PK analysis. These CYPs were chosen for investigation on the basis of the rank order of relative biotransformation activity for 10 µM ixazomib of the major human CYP isozymes, where they contributed >25% to the metabolism of ixazomib in recombinant CYPs.

Ixazomib Cmax and AUC were similar when ixazomib was co-administered with or without a strong CYP3A inhibitor (clarithromycin). The geometric least squares mean ratios (90% CIs) for Cmax and AUC were 0.96 (0.67-1.36) and 1.11 (0.86-1.43), respectively, indicating that clarithromycin did not have a clinically meaningful effect on the PK of ixazomib. **No dose adjustment is necessary when ixazomib is co-administered with strong CYP3A inhibitors**.

The effect of strong CYP1A2 inhibitors (eg, ciprofloxacin) on the PK of ixazomib was examined in the population PK analysis as a time-dependent categorical covariate. On the basis of covariate analysis, CYP-modulatory drugs, including strong CYP1A2 inhibitors, had no statistically significant effect on the PK of ixazomib. **No dose adjustment is necessary when ixazomib is co-administered with strong CYP1A2 inhibitors**.

6.1.3.2 CYP Inducers

The effect of rifampicin, a pleiotropic inducer of multiple pregnane X receptor (PXR)-inducible drug-metabolizing enzymes and transporters and an established strong CYP3A inducer, on the PK of ixazomib was examined in a dedicated clinical study (C16009 Arm 4). Ixazomib Cmax was reduced in the presence of rifampicin by approximately 54%; corresponding geometric least squares mean ratio (90% CI) of 0.46 (0.29-0.73). Ixazomib AUC was reduced by approximately 74%; corresponding least squares geometric mean ratio (90% CI) of 0.26 (0.18-0.37). On the basis of these data, **the co-administration of strong CYP3A inducers (such as carbamazepine, phenytoin, rifampicin, and St. John's wort) with ixazomib should be avoided**.

6.1.3.3 Effect of Ixazomib on Other Drugs and Transporter-Based Interactions

Ixazomib is neither a time-dependent nor reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 (IC50 >30 μM, inhibitory concentration [Ki] >15 μM); therefore, the potential for ixazomib to produce drug-drug interactions via CYP isozyme inhibition is low.

Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4 activity or corresponding immunoreactive protein levels under conditions where prototypical inducers caused anticipated increases in CYP activity (with ixazomib concentrations up to 9.67 μM). Therefore, ixazomib is unlikely to produce drug-drug interactions via induction of metabolism- or transporter-mediated CL of co-administered drugs, as it did not induce expression of any of the representative sensitive downstream CYP enzymes that are induced via the arylhydrocarbon receptor (eg, CYP1A2), constitutive androstane receptor (eg, CYP2B6), or PXR (eg, CYP3A4/5).

Ixazomib is not a substrate of BCRP, MRP2, and OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, multidrug and toxin extrusions protein (MATE) 1, and MATE2-K. Ixazomib is unlikely to cause or be susceptible to clinical drug-drug interactions with substrates or inhibitors of clinically relevant drug transporters.

6.1.4 Toxicity/Adverse Events

As of 27March2022, the overall safety population in oncology studies comprises 3360 patients in phase 1 to 3 studies who have received at least 1 dose of ixazomib or placebo in ongoing and completed open-label or unblinded studies. Safety data is available from 1974 patients who have received at least 1 dose of ixazomib in open-label or unblinded studies, regardless of route of administration.

Study C16010, a global, pivotal, phase 3, double-blind multicenter trial in patients with relapsed/refractory MM, was conducted to evaluate the safety of ixazomib when added to LenDex as the background chemotherapeutic regimen. At the primary analysis, the median age of enrolled patients was 66 years (range 30–91 years). Given the advanced age (median of 70 years) of patients with MM at diagnosis,[52] distinguishing between disease-related and treatment-related AEs in nonrandomized clinical trials is difficult because of the multiple co-morbidities in patients or overlapping toxicities of the background regimen; therefore, the results of this double-blind, placebo-controlled study are informative to characterize the safety of the addition of ixazomib to the background regimen.

At the final analysis as of the data cut off date of 28September2020, the percentage of patients reporting at least 1 treatment-emergent AE (TEAE) was similar between the ixazomib regimen and placebo regimen, with incidence rates of 99% for both, consistent with an oncology setting where

patients' life-threatening disease is being treated with cytotoxic therapy. Grade ≥3 TEAEs were reported in 80% of patients in the ixazomib regimen and 74% of patients in the placebo regimen. The frequency of serious AEs was 57% and 56%, respectively, with 21 (6%) and 30 (8%) on-study deaths, respectively. The frequency of TEAEs resulting in treatment discontinuation (discontinuation of all 3 agents) was similar between the regimens (25% ixazomib regimen; 22% placebo regimen), suggesting that ixazomib does not add substantial toxicity to the background regimen. The most frequently reported AEs are noted in Table 2. The most frequently reported treatment-related serious adverse event (SAE) in both the ixazomib and placebo regimen was pneumonia (6% and 8%, respectively).

Table 2 The most frequently reported AE (≥20%) in patients with relapsed/refractory MM

Adverse Events	Ixazomib	Placebo
Diarrhea	52%	43%
Constipation	35%	28%
Anemia	35%	31%
Fatigue	32%	29%
Nausea	32%	23%
Neutropenia	31%	28%
Thrombocytopenia	28%	13%
Back pain	27%	24%
Upper respiratory tract infection	27%	23%
Peripheral edema	27%	21%
Vomiting	26%	13%
Nasopharyngitis	25%	24%
Peripheral sensory neuropathy	24%	17%
Insomnia	23%	30%
Pneumonia	22%	20%
Bronchitis	22%	17%
Cough	20%	18%
Muscle spasms	19%	28%
Pyrexia	18%	22%

Data from the pivotal phase 3 Study C16010 demonstrated that some AEs (eg, thrombocytopenia, nausea, vomiting, diarrhea, and rash) are overlapping toxicities with ixazomib and lenalidomide. While some TEAE categories (eg, thrombocytopenia, nausea, vomiting, diarrhea, and rash,peripheral neuropathy, and bronchitis) occurred more frequently (difference of at least 5 percentage points) in the ixazomib regimen than in the placebo regimen, they were predominantly low grade, manageable with supportive care and dose modification, and generally did not lead to more treatment discontinuations with ixazomib.

Overall, ixazomib in combination with LenDex did not substantially increase toxicity of the background regimen and there was no evidence of cumulative or long-term toxicity after a median follow-up of approximately 7 years as of the data cutoff date of 28September2020. The TEAEs were consistent with the reported safety profile of the individual agents in the combination regimen and were tolerable and manageable.

Per the currently approved Ixazomib Investigator's Brochure edition 15 dated 25May2022, important identified risks associated with ixazomib treatment include rash, nausea, vomiting, diarrhea, thrombocytopenia, and peripheral neuropathy. Important potential risks include the uncommon risk of Stevens-Johnson Syndrome, and the rare risk of toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, and

pemphigus vulgaris. All of these important identified and potential risks associated with ixazomib use have been managed by routine risk minimization measures (product labeling) and routine pharmacovigilance measures.

Clinical investigations into the potential benefit of ixazomib are ongoing through a comprehensive and global development plan that involves several company-sponsored clinical studies.

6.1.5 Pregnancy and Nursing Mothers

In an embryo-fetal development study in pregnant rabbits there were increases in fetal skeletal variations/abnormalities at doses that were also maternally toxic. In a rat dose range-finding embryo-fetal development study, at doses that were maternally toxic, there were decreases in fetal weights, a trend toward decreased fetal viability, and increased postimplantation losses.

Embryo-fetal lethality has been observed in rats and rabbits with other proteasome inhibitors (such as bortezomib and carfilzomib)[53,54] at doses that are minimally toxic to dams. On the basis of the data with ixazomib and other drugs in this class, there is the potential for embryo-fetal effects in humans with ixazomib.

Fertility and prenatal and postnatal development studies have not been performed.
Additional details are available in Sections 4.3.4 of the Investigator Brochure.

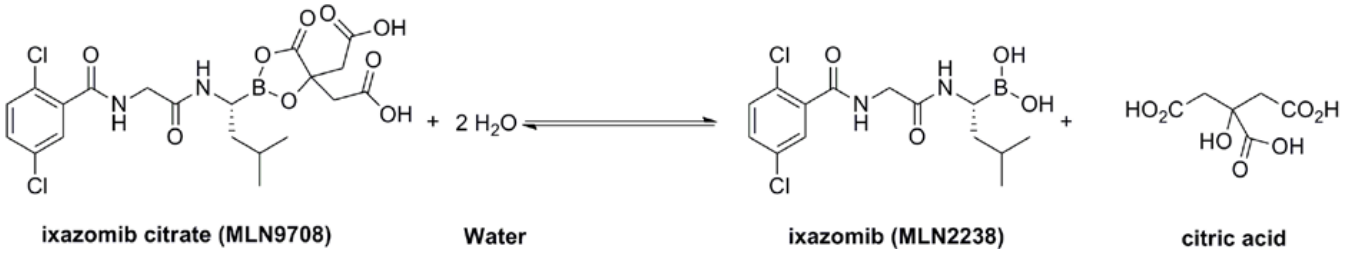
6.1.6 Formulation, Preparation and Stability

Ixazomib drug product has been developed for use in clinical studies as both a parenteral lyophilized powder for injection formulation and as an oral solid (immediate release capsule) dosage formulation. The parenteral lyophilized formulation of ixazomib, *MLN9708 Powder for Solution for Injection*, has been previously investigated in adult clinical trials (Studies C16001 and C16002) and is considered suitable for the pediatric population as it can be administered in varying doses based on body surface area (BSA) to all age groups.

The parenteral dosage form, *MLN9708 Powder for Solution for Injection*, is a lyophilized powder consisting of 5.72 mg of ixazomib citrate (equivalent to 4.0 mg of ixazomib), citric acid monohydrate, sodium citrate dihydrate and glycine as excipients in a single use glass vial.

The solution structure of ixazomib citrate was also evaluated in aqueous solution in the presence of excess citric acid. A high percentage of the ester structure is maintained due to the presence of excess of citric acid. Under physiological conditions, ixazomib citrate rapidly hydrolyzes to ixazomib (Figure 2). Ixazomib is the biologically active, boronic acid form of ixazomib citrate.

Figure 2 Hydrolysis of ixazomib citrate (MLN 9708) to ixazomib (MLN 2238)



The use of the lyophilized formulation for clinical studies is supported by available long term stability data. Satisfactory stability was demonstrated up to 60 months when stored at 5°C ±3°C.

The ixazomib capsule formulation consists of ixazomib citrate and common pharmaceutical excipients, including microcrystalline cellulose, talc, and magnesium stearate encapsulated in a hard gelatin capsule for oral administration. A total of 7 different capsule strengths consisting of 0.2, 0.5, 2.0, 2.3, 3.0, 4.0, and 5.5 mg of biologically active ixazomib have been developed for the clinical studies. Capsule strengths are differentiated by unique capsule shell color. Ixazomib capsules corresponding to 0.2, 0.5, and 2.0 mg strengths are currently being investigated in multiple clinical studies whereas 2.3, 3.0, and 4.0 mg ixazomib capsule strengths are registered for commercialization.

6.1.7 Supplier

Ixazomib will be supplied by Takeda Pharmaceuticals.

Ingredient	**mg per Capsule**					
	0.2-mg	**0.5-mg**	**2.0-mg**	**2.3-mg**	**3.0-mg**	**4.0-mg**
Capsule Appearance	Size 4, White opaque	Size 3, Dark green	Size 2, Swedish orange	Size 4, Flesh/light pink	Size 4, Light grey	Size 3, Ivory opaque
Package Size	1x4 blister strips, 24 count	1x4 blister strips, 24 count	1x4 blister strips, 24 count	1x3 blister strips, 3 count	1x3 blister strips, 3 count	1x3 blister strips, 3 count

6.1.8 **Guidelines for Administration**

Ixazomib capsules and oral solution should be administered on an empty stomach, at least 1 hour before or at least 2 hours after food. If ixazomib cannot be administered on an empty stomach, the timing of food intake relative to ixazomib administration should be recorded.

Capsule administration:

Ixazomib capsules will be supplied by the sponsor as single capsules at 6 different dose strengths, containing 4.0, 3.0, 2.3, 2.0, 0.5 and 0.2 mg of ixazomib. Ixazomib capsule is dispensed in blisters in a child-resistant carton. For the 2.3, 3.0, and 4.0 mg capsule strengths, there are 3 capsules in each wallet/carton. For patients receiving capsules, the BSA-based dose should be rounded to the nearest 0.2mg.

Patients should be instructed to swallow ixazomib capsules whole with water and not to break, chew, or open the capsules. The capsule should be swallowed with a sip of water. A total of up to approximately 20-50 mL of water should be taken with the capsules. Under circumstances where home dosing is allowed, a missed dose can be taken as soon as the patient/parent remembers, as long as the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose. Please refer to the Pharmacy Manual for detailed instructions.

Oral solution administration:

MLN9708 Powder for Solution for Injection will be supplied as a lyophilized drug product vial consisting of 5.72 mg of ixazomib citrate (equivalent to 4.0 mg of ixazomib).

The investigational pharmacist will prepare the study treatment for ixazomib oral solution in drug product. For preparation of the active ixazomib treatment, each vial of *MLN9708 Powder for Solution for Injection* should be equilibrated at ambient temperature and reconstituted with 4.4 mL of water to 1.0 mg/ml. The drug product upon reconstitution should be administered within 4 hours, the reconstituted drug product would be further diluted with flavoring agent. The required dose should be administered to the patient by mouth [(or via nasogastric tube when clinically indicated)] via oral syringe, and should be followed by approximately 20 – 50 ml of water. Please refer to the Pharmacy Manual for detailed instructions.

Handling precautions:

Ixazomib is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised during handling. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during clean-up and during return of broken capsules and powder to minimize skin contact. The area should be ventilated and the site washed with soap and water after material pick up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule) or reconstituted oral solution, skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Please refer to the Pharmacy Manual for detailed instructions.

6.1.9 **Storage, Handling, and Accountability**

On receipt at the investigative site, ixazomib capsules should remain in the blister and carton provided until use or dispensation. The ixazomib drug product is to be stored in a secure facility with controlled access. The *MLN9708 Powder for Solution for Injection* vial must be stored refrigerated at 2˚C to 8˚C (36˚F to 46˚F). A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. All excursions from the temperature storage guidelines should be brought to the sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In the event that take-home dosing of ixazomib capsules is allowed, the capsule dispensed to the patient should remain in the blister packaging and carton and stored as directed until the point of use. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients should be instructed to return their empty or partially used cartons to the investigative site at their next visit, rather than discarding them, as permitted by site policy. Reconciliation will occur accordingly when the patient returns at their next visit for take-home medication. Any excursions in temperature should be reported and dealt with on a case-by-case basis. Please refer to the Pharmacy Manual for detailed instructions.

6.2 ASPARAGINASE or crisantaspase (Erwinase®) or Erwinia chrysanthemi (recombinant)-rywn (Rylaze®)

6.2.1 Source and Pharmacology:

L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. Neoplastic cells associated with acute lymphoblastic leukemia, acute myeloid leukemia and lymphoblastic lymphosarcoma are asparagine-dependent but lack asparagine synthetase activity. The administration of L-asparaginase produces an anti-neoplastic effect by catalyzing asparagine into aspartic acid and ammonia. As a result, these cells lack the ability to produce the asparagine necessary for protein metabolism and survival. Deamination of glutamine may also play a role in the antineoplastic activity of asparaginase.

Asparaginase *Erwinia chrysanthemi* (ErwinazeTM) is asparaginase derived from cultures of *Erwinia chrysanthemi*. L-asparaginase is a tetrameric enzyme; each of the four identical subunits has a molecular weight of approximately 35 kDa. Asparaginase *Erwinia chrysanthemi* is immunologically distinct from *E. coli* L-asparaginase and may allow continued asparaginase therapy when a hypersensitivity reaction occurs to *Escherichia coli*-derived asparaginase. The package labeling states that there is insufficient information to characterize the incidence of antibodies to asparaginase *Erwinia chrysanthemi*. Several factors are involved in immunogenicity assay results and the assessment of antibodies, including assay methodology, assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medications, and the underlying disease state. The following data have been reported on each of the three preparations of asparaginase:

Clinical Pharmacology of Asparaginase Formulation	**Elimination half-life (IM)**	**% Anti-Asparaginase Antibody positive patients**
Native *Escherichia Coli*	26-30 hours	45-75
Pegylated-asparaginase	5.5-7 days	5-18
Erwinia Asparaginase	16 hours (7-13 hrs package insert)	30-50

From: Avramis, V; Panosyan, E; Pharmacokinetic/Pharmacodynamic Relationships of Asparaginase Formulations: The Past, the Present and Recommendations for the Future. Clin Pharmacokinet 2005; 44 (4): 367-393.

Effective asparaginase levels have been defined as activity of ≥ 0.1 International Units per mL. Clinical trials with asparaginase *Erwinia chrysanthemi* demonstrated that 100% of patients achieved effective asparaginase levels at 48 and 72 hours (n=35 and n=13, respectively) following the third total dose when given on a Monday, Wednesday, Friday schedule. No formal drug interaction studies have been performed with asparaginase *Erwinia chrysanthemi*.

Asparaginase erwinia chrysanthemi (recombinant)-rywn contains an asparagine specific bacterial enzyme (L-asparaginase). L-asparaginase is a tetrameric enzyme that consists of four identical 35 kDa subunits with a combined molecular weight of 140 kDa. The amino acid sequence is identical to native asparaginase *Erwinia chrystanthemi* (also known as crisantaspase). The activity of asparaginase erwinia chrysanthemi (recombinant)-rywn is expressed in units, defined as the amount of enzyme that catalyzes the conversion of 1µmol of L-asparagine per reaction minute, per mg of protein. Asparaginase erwinia chrysanthemi (recombinant)-rywn is produced by fermentation of a genetically engineered *Pseudomonas fluorescens* bacterium containing the DNA which encodes for asparaginase *Erwinia chrysanthemi*.

6.2.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Allergic reactions, anaphylaxis, urticaria	Local injection site reactions, fever
Prompt: Within 2-3 weeks, prior to the next course			Pancreatitis, glucose intolerance, thrombosis, hemorrhage, transient ischemic attack, disseminated intravascular coagulation, hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, hyperglycemia, hyperammonemia, vomiting, nausea, abdominal pain, headache, diarrhea, seizure
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of L-asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk. Adequate, well-controlled studies of asparaginase *Erwinia chrysanthemi* have NOT been conducted. It is not known whether asparaginase *Erwinia chrysanthemi* will cause fetal harm or affect the ability to reproduce. It is not known if asparaginase *Erwinia chrysanthemi* is excreted into breast milk. The use of asparaginase *Erwinia chrysanthemi* should be avoided in pregnant or lactating patients.		

6.2.3 Formulation and Stability

Asparaginase *Erwinia chrysanthemi* is supplied as a sterile, white lyophilized powder for reconstitution in a clear glass vial with a 3 mL capacity. Each vial contains 10,000 International Units of asparaginase *Erwinia chrysanthemi* and the following inactive ingredients: glucose monohydrate (5.0 mg), sodium chloride (0.5 mg). Store intact vials between 2°C and 8°C (36° to 46ºF). Protect from light.

Asparaginase erwinia chrysanthemi (recombinant)-rywn) Rylaze®) injection is supplied as a sterile, clear to opalescent, colorless to slightly yellow, preservative-free solution for intramuscular injection. Each 0.5 mL contains 10 mg asparaginase erwinia chrysanthemi (recombinant)-rywn and the inactive ingredients: polysorbate 80 (0.1 mg), sodium chloride (1.5 mg), sodium phosphate dibasic anhydrous (0.8 mg), sodium phosphate monobasic monohydrate (0.6 mg), and trehalose (32.1 mg). Sodium hydroxide may be added to adjust the pH. The pH is approximately 7.

6.2.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

Use appropriate precautions for preparation of a hazardous agent. Visually inspect the powder in vial for foreign particles or discoloration prior to reconstitution. The contents of each vial should be reconstituted by slowly adding 1 mL or 2 mL of sterile, preservative-free NS to the inner vial wall. The final concentration is 10,000 International Units per mL when using 1 mL for reconstitution or 5,000 International Units per mL when using 2 mL for reconstitution. Gently mix or swirl the contents

to dissolve the contents of the vial. Do not shake or invert the vial. The resulting solution should be clear and colorless. Discard if any particulate matter or protein aggregates are visible. **Withdraw the appropriate dosing volume into a polypropylene syringe within 15 minutes of reconstitution.** Polycarbonate luer-lok syringes from B-D (1 mL) are also acceptable (personal communication, EUSA Pharma). Discard any unused drug; do not save or use any unused drug remaining the in the vial.

Administer the dose within a 4 hour time period from reconstitution. If the dose is not used within this time period, discard the dose. Do not freeze or refrigerate the reconstituted solution.

Administer the dose intramuscularly (IM). No more than 2 mL should be given at any one injection site. Doses larger than 2 mL should be divided and given in separate administration sites.

6.2.5 Supplier

Commercially available. See package insert for further information.

6.3 CYCLOPHOSHAMIDE - INJECTIONCYCLOPHOSPHAMIDE - INJECTION

6.3.1 Source and Pharmacology

Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent *in vitro* than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

6.3.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia	Amenorrhea1	Gonadal dysfunction: ovarian failure1 (L), interstitial pneumonitis, pulmonary fibrosis2 (L)

	(prolonged or permanent)1 (L)		
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

1 Dependent on dose, age, gender, and degree of pubertal development at time of treatment.
2 Risk increased with pulmonary chest irradiation and higher doses.
(L) Toxicity may also occur later.

6.3.3 Formulation and Stability

Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30ºC (86ºF).

6.3.4 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

Cyclophosphamide for Injection: Reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. If administered as undiluted drug at the 20 mg/mL concentration, reconstitute with NS only to avoid a hypotonic solution. Solutions reconstituted with preservative should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration.

Cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use.

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

6.4 DOXORUBICIN (Adriamycin®) NSC #123127 (05/09/11)

6.4.1 Source and Pharmacology

An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the

hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

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

6.4.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva	Hyperuricemia, facial flushing, sclerosis of the vein	Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, conjunctivitis and lacrimation
Delayed: Any time later during therapy		Cardiomyopathy[1] (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m²) *(L)*	Cardiomyopathy[1] (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m²) *(L)*, ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis
Late: Any time after completion of treatment	Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients)	Secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans		

[1] Risk increases with cardiac irradiation, exposure at a young or advanced age.
(L) Toxicity may also occur later.

6.4.3 Formulation and Stability

Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1] vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 200 mg[2] vials.
[1] Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF (rapid dissolution formula) also contains methylparaben, 1 mg per each 10 mg of doxorubicin, to enhance dissolution.
[2] Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.

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

Powder for Injection: Store unreconstituted vial at room temperature, 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration, 2°-8°C (36°-46°F) when protected from light. Doxorubicin further diluted in 50 – 1000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

6.4.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

Administer IV through the tubing of rapidly infusing solution of D5W or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

6.4.5 Supplier

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

6.5 ETOPOSIDE – INJECTION

(VePesid®, Etopophos®, VP-16) NSC #141540 (05/09/11)

6.5.1 Source and Pharmacology

A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in single and double strand DNA breaks. Its main effect appears to be in the S and G2 phase of the cell cycle. The initial t½ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the non-renal clearance of etoposide.

The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. There is poor diffusion into the CSF < 5%.

Etoposide phosphate is a water soluble ester of etoposide which is rapidly and completely converted to etoposide in plasma. Pharmacokinetic and pharmacodynamic data indicate that

etoposide phosphate is bioequivalent to etoposide when it is administered in molar equivalent doses.

6.5.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, leukopenia), alopecia	Thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticarial	Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis
Delayed:	Any time later during therapy		Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late:	Any time after completion of treatment		Secondary malignancy (preleukemic or leukemic syndromes)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20th of the human dose. It is unknown whether the drug is excreted in breast milk.		

6.5.3 Formulation and Stability

Etoposide for Injection is available as a 20 mg/mL solution in sterile multiple dose vials (5 mL, 25 mL, or 50 mL each). The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen. Unopened vials of etoposide are stable until expiration date on package at controlled room temperature (20˚-25˚C or 68˚-77˚F).

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate *USP*, and 300 mg dextran 40. Etoposide phosphate must be stored under refrigeration (2°-8°C or 36°-46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

6.5.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.
<u>Etoposide:</u>

Dilute etoposide to a final concentration ≤ 0.4 mg/mL in D5W or NS. Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2 mg/mL; stability is 24 hours at room temperature with concentrations of 0.4 mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4 mg/mL. Use in-line filter during infusion secondary to the risk

of precipitate formation. However, the use of an in-line filter is not mandatory since etoposide precipitation is unlikely at concentrations of 0.1-0.4 mg/mL. **Do not administer etoposide by rapid intravenous injection.** Slow rate of administration if hypotension occurs.

Leaching of diethylhexyl phthalate (DEHP) from polyvinyl chloride (PVC) bags occurred with etoposide 0.4 mg/mL in NS. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy; glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used to minimize exposure to DEHP.

Etoposide Phosphate:

Reconstitute the 100 mg vial with 5 or 10 mL of Sterile Water for Injection, D5W, NS, Bacteriostatic Water for Injection with Benzyl Alcohol, or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide equivalent (22.7 mg/mL or 11.4 mg/mL etoposide phosphate), respectively. **Use diluents without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.**

When reconstituted as directed, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration for 7 days. When reconstituted with a diluent containing a bacteriostat, store at controlled room temperature for up to 48 hours. Following reconstitution with SWFI, D5W, or NS, store at controlled room temperature for up to 24 hours.

Following reconstitution, etoposide phosphate may be further diluted to a concentration as low as 0.1 mg/mL of etoposide with D5W or NS.. The diluted solution can be stored under refrigeration or at controlled room temperature for 24 hours.

6.5.5 Supplier

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

6.6 INTRATHECAL TRIPLE (Methotrexate/Hydrocortisone/Cytarabine)

6.6.1 Source and Pharmacology

The intrathecal route of administration of a drug produces more consistent CSF drug concentrations at relatively smaller doses because of the volume difference between the CSF and blood compartments (140 mL vs. 3500 mL in an adult). (The CSF volume of children after the first 3 years is equivalent to that of an adult). Drug half-lives are longer as well because clearance is related to flow rather than metabolism or protein binding. Intrathecal methotrexate has a biphasic elimination curve from the CSF with a t½ of 4.5 and 14 hours respectively. Following IT injection of cytarabine the elimination of the drug from the CSF is biphasic with a t½ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

6.6.2 Toxicity

	Common Happens to 21-100 children	**Occasional**	**Rare** Happens to < 5 children out of every 100

	out of every 100	Happens to 5-20 children out of every 100	
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoditis: (headache, fever, vomiting, meningismus and pleocytosis)	Rash, anaphylaxis *(L)*, paresis, bleeding into subarachnoid or subdural space (risk > with platelet counts <20,000), confusion, fatigue, disorientation, seizures
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, somnolence, ataxia, cranial nerve palsy, transient and rarely permanent paraplegia *(L)*, speech disorders
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances *(L)*, learning disabilities *(L)*	Demyelating leukoencephalopathy[1] *(L)*, blindness[1]
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] May be enhanced by systemic therapy such as high dose methotrexate or cytarabine and/or cranial irradiation.
(L) Toxicity may also occur later.

6.6.3 Formulation and Stability

Methotrexate 25 mg/mL **preservative free** 2 mL vial or methotrexate 20 mg preservative free sterile powder for injection vial. Cytarabine 100 mg preservative free sterile powder for injection. Hydrocortisone sodium succinate100 mg vial sterile powder for injection.

6.6.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.
For intrathecal administration, dilute each agent with 5-10 mL preservative free NS, lactated ringers or Elliot's B solution or as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	Doses (MTX/hydrocortisone/ Ara-C)	Recommended volume	10% CSF volume	CSF Volume
1 – 1.99	8 mg / 8 mg / 16 mg	5-10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	10 mg / 10 mg / 20 mg	5-10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	12 mg / 12 mg / 24 mg	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	15 mg / 15 mg / 30 mg	5-10 mL	13 mL	130 ± 30 mL (adults)

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal triples are stable in NS for 24 hours at 25ºC but contain no preservative and should be administered as soon as possible after preparation.

6.6.5 Supplier

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

6.7 LEUCOVORIN CALCIUM (LCV, Wellcovorin®, citrovorum factor, folinic acid) NSC #003590 (05/09/11)

6.7.1 Source and Pharmacology

Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)- l-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of “one-carbon” moieties. Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid (an active metabolite of 5-FU) to thymidylate synthase and thereby enhances the inhibition of this enzyme. Peak serum levels of 5-methyl THF (an active metabolite) were reached at approximately 1.3-1.5 hours (IV/IM) and 2.3 hours for the oral form. The terminal half-life of total reduced folates was approximately 6.2 hours. Following oral administration, leucovorin is rapidly absorbed and expands the serum pool of reduced folates. At a dose of 25 mg, almost 100% of the *l*-isomer (the biologically active form) but only 20% of the *d*-isomer is absorbed. Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg doses. Both oral and parenteral leucovorin raise the CSF folate levels.

6.7.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug			Anaphylaxis, 63rticarial, seizure
Unknown Frequency and timing:	Fetal toxicities and teratogenic effects of leucovorin in humans are unknown. It is unknown whether the drug is excreted in breast milk.		

6.7.3 Formulation and Stability

Leucovorin calcium for injection is supplied as a sterile ready to use liquid and a sterile powder for injection. The 10 mg/mL preservative free liquid is available in 50 mL vials containing sodium chloride 400 mg/vial. Store preservative free liquid in the refrigerator at 2°-8°C (36°-46°F) protected from light. The powder for injection is available in 50 mg, 100 mg, 200 mg, and 350 mg vials. Store at room temperature 15°-25°C (59°-77°F) protected from light. Reconstitute the sterile powder with sterile water for injection or bacteriostatic water for injection to a concentration of 10 mg/mL leucovorin calcium. **Do not use diluents containing benzyl alcohol for doses > 10 mg/m² or in**

infants < 2 years of age or patients with allergy to benzyl alcohol. When Bacteriostatic Water is used, the reconstituted solution is good for 7 days. If reconstituted with SWFI, use solution immediately as it contains no preservative. One milligram of leucovorin calcium contains 0.004 mEq of leucovorin and 0.004 mEq of calcium.

The oral form of leucovorin is available as 5 mg, 10 mg, 15 mg, and 25 mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: corn starch, dibasic calcium phosphate, magnesium stearate, pregelatinized starch, lactose, microcrystalline cellulose, and sodium starch glycolate.

6.7.4 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

Injection:
Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral:
Oral leucovorin should be spaced evenly (e.g., every six hours) throughout the day and may be taken without regard to meals. Doses > 25 mg should be given IV due to the saturation of absorption.

Leucovorin should not be administered < 24 hours after intrathecal injections which contain methotrexate unless there are special circumstances.

6.7.5 Supplier

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

6.8 METHOTREXATE (MTX, amethopterin) NSC #000740 (02/29/12)

6.8.1 Source and Pharmacology

A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1 µmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half-life of 8-15 hours. About 50% is bound to protein. The elimination of MTX from the CSF after an intrathecal dose is characterized by a biphasic curve with half-lives of 4.5 and 14 hours. After intrathecal administration of 12 mg/m², the lumbar concentration of MTX is ~100 times higher than in plasma. (Ventricular concentration is ~ 10% of lumbar concentration). MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic

circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and 65scetic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

6.8.2 Toxicity

[1] May be enhanced by HDMTX and/or cranial irradiation.

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Transaminase elevations	Nausea, vomiting, anorexia	Anaphylaxis, chills, fever, dizziness, malaise, drowsiness, blurred vision, acral erythema, urticaria, pruritis, toxic epidermal necrolysis, Stevens-Johnson Syndrome, tumor lysis syndrome, seizures[1], photosensitivity
Prompt: Within 2-3 weeks, prior to the next course		Myelosuppression, stomatitis, gingivitis, photosensitivity, fatigue	Alopecia, folliculitis, acne, renal toxicity (ATN, increased creatinine/BUN, hematuria), enteritis, GI ulceration and bleeding, acute neurotoxicity[1] (headache, drowsiness, aphasia, paresis, blurred vision, transient blindness, dysarthria, hemiparesis, decreased reflexes) diarrhea, conjunctivitis
Delayed: Any time later during therapy, excluding the above conditions		Learning disability[1] *(L)*	Pneumonitis, pulmonary fibrosis *(L)*, hepatic fibrosis *(L)*, osteonecrosis *(L)*, leukoencephalopathy[1] *(L)*, pericarditis, pericardial effusions, hyperpigmentation of the nails
Late: Any time after the completion of therapy			Progressive CNS deterioration[1]
Unknown Frequency and Timing:	Methotrexate crosses the placenta. Fetal toxicities and teratogenic effects of methotrexate have been noted in humans. The toxicities include: congenital defects, chromosomal abnormalities, severe newborn myelosuppression, low birth weight, abortion, and fetal death. Methotrexate is excreted into breast milk in low concentrations		

(L) Toxicity may also occur later.

Intrathecal Therapy (Methotrexate Single Agent) Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, headache	Arachnoditis: (headache, fever, vomiting, meningismus, nuchal rigidity, and pleocytosis)	Anaphylaxis, vomiting, seizures *(L)*, malaise, confusion, back pain, rash, bleeding into subarachnoid or subdural space (risk > with platelet counts < 20,000)

Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia, somnolence, cranial nerve palsy, subacute myelopathy (paraparesis/ paraplegia), speech disorders, pain in the legs, bladder dysfunction
Delayed:	Any time later during therapy, excluding the above condition	Cognitive disturbances *(L)*[1], learning disability *(L)*[1]	Leukoencephalopathy[1] *(L)*
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] May be enhanced by HDMTX and/or cranial irradiation.
(L) Toxicity may also occur later.

6.8.3 Formulation and Stability

Methotrexate for Injection is available as a lyophilized powder for injection in 1000 mg vials. The powder for injection contains approximately 7 mEq sodium in the 1000 mg vial. Methotrexate for Injection is also available as a 25 mg/mL solution in 2, 4, 8, 10, and 40 mL preservative free vials and 2 and 10 mL vials with preservative. The 2, 4, 8, 10, and 40 mL solutions contain approximately 0.43, 0.86, 1.72, 2.15, and 8.6 mEq sodium per vial, respectively. The preserved vials contain 0.9% benzyl alcohol as a preservative**.**
Sterile methotrexate powder or solution is stable at 20º-25ºC (68º-77ºF); excursions permitted to 15º-30ºC (59º- 86ºF). Protect from light.

6.8.4 Guidelines for Administration

See Treatment and Dose Modifications sections of protocol. Leucovorin rescue may be necessary with certain doses of methotrexate.

For IM/IV use: Powder for injection: Dilute 1000 mg vial with 19.4 mL of preservative free SWFI, D5W or NS to a 50 mg/mL concentration. The powder for injection may be further diluted in NS or dextrose containing solutions to a concentration of ≤ 25 mg/mL for IV use.

The 25 mg/mL solution may be given directly for IM administration or further diluted in Saline or Dextrose containing solutions for IV use. **Do not use the preserved solution for high dose or intermediate dose methotrexate administration due to risk of benzyl alcohol toxicity.** Methotrexate dilutions are chemically stable for at least 7 days at room temperature but contain no preservative and should be used within 24 hours. Diluted solutions especially those containing bicarbonate exposed to direct sunlight for periods exceeding 4 hours should be protected from light.

High dose and intermediate dose methotrexate requires alkalinization of the urine, adequate hydration and leucovorin rescue. Avoid probenecid, penicillins, cephalosporins, aspirin, proton pump inhibitors, and NSAIDS as renal excretion of MTX is inhibited by these agents.

For Intrathecal use: Use **preservative free** 25 mg/mL solution.

For intrathecal administration, dilute with 5-10 mL preservative free NS, lactated Ringer's, or Elliot's B solution as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	Methotrexate dose	Recommended volume	10% CSF volume	CSF Volume 109
1–1.99	8 mg	5–10 mL	5 mL	50 + 10 mL (babies)
2–2.99	10 mg	5-10 mL	8 mL	80 + 20 mL (younger children)
3–8.99	12 mg	5-10 mL	10 mL	100 + 20 mL (older children)
9 or greater	15 mg	5-10 mL	13 mL	130 + 30 mL (adults)

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Diluted methotrexate for intrathecal administration is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

6.8.5 Supplier

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

6.9 PEGASPARGASE (PEG-asparaginase, PEGLA, PEG-L-asparaginase, polyethylene glycol-L-asparaginase, Oncaspar®) NSC #624239 (05/09/11)

6.9.1 Source and Pharmacology

Pegaspargase is a modified version of the enzyme L-asparaginase. L-asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of Pegaspargase is derived from *Escherichia coli* which is purchased in bulk from Merck, Sharp and Dohme. L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. The ability to synthesize asparagine is notably lacking in malignancies of lymphoid origin. Asparaginase depletes L-asparagine from leukemic cells (especially lymphoblasts) by catalyzing the conversion of L-asparagine to aspartic acid and ammonia. In predominately L-asparaginase naïve adult patients with leukemia and lymphoma, initial plasma levels of L-asparaginase following intravenous administration of pegaspargase were determined. Apparent volume of distribution was equal to estimated plasma volume. L-asparaginase was measurable for at least 15 days following the initial treatment with Pegaspargase. The approximate t½ in adult patients is 5.73 days. The enzyme could not be detected in the urine. The half-life is independent of the dose administered, disease status, renal or hepatic function, age, or gender. In a study of newly diagnosed pediatric patients with ALL who received either a single intramuscular injection of pegaspargase (2500 IU/m2), *E. coli* L-asparaginase (25000 IU/m2), or *Erwinia* (25000 IU/m2), the plasma half-lives for the three forms of L-asparaginase were: 5.73 ± 3.24 days, 1.24 ± 0.17 days, and 0.65 ± 0.13 days respectively. The plasma half-life of pegaspargase is shortened in patients who are previously hypersensitive to native L-asparaginase as compared to non-hypersensitive patients. L-asparaginase is cleared by the reticuloendothelial system and very little is excreted in the urine or bile. Cerebrospinal fluid levels are < 1% of plasma levels.

6.9.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Allergic reactions (total likelihood of local, and or systemic reaction especially if previous hypersensitivity reaction to native asparaginase), pain at injection site, weakness, fatigue, diarrhea	Allergic reactions (total likelihood of local, and or systemic reaction if **no** previous hypersensitivity reaction to native asparaginase), rash	Anaphylaxis, hyper/hypotension, tachycardia, periorbital edema, chills, fever, dizziness, dyspnea, bronchospasm, lip edema, arthralgia, myalgia, urticaria, mild nausea/vomiting, abdominal pain, flatulence, somnolence, lethargy, headache, seizures *(L)*, hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Hyperammonemia *(L)*, coagulation abnormalities with prolonged PTT, PT and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III & other clotting factors) *(L)*	Hyperglycemia, abnormal liver function tests, pancreatitis *(L)*, increased serum lipase/amylase	Hemorrhage *(L)*, DIC, thrombosis, anorexia, weight loss, CNS ischemic attacks, edema, azotemia and decreased renal function, mild leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, hemolytic anemia, infections (sepsis with/without septic shock, subacute bacterial endocarditis [SBE], URI), CNS changes including irritability, depression, confusion, EEG changes, hallucinations, coma and stupor, paresthesias, hypertriglyceridemia, hyperlipidemia, Parkinson-like syndrome with tremor and increase in muscular tone, hyperbilirubinemia, chest pain
Delayed: Any time later during therapy			Renal failure, urinary frequency, hemorrhagic cystitis, elevated creatinine and BUN, fatty liver deposits, hepatomegaly, liver failure
Unknown Frequency and Timing:	Animal reproduction studies have not been conducted with pegaspargase. It is not known whether pegaspargase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, fetal toxicities and teratogenic effects of asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

(L) Toxicity may also occur later.

6.9.3 Formulation and Stability

Each milliliter of pegaspargase contains: PEG-L-asparaginase 750 IU ± 20%, monobasic sodium phosphate, *USP* 1.20 mg ± 5% dibasic sodium phosphate, *USP* 5.58 mg ± 5%, sodium chloride, *USP* 8.50 mg ± 5% , Water for Injection, *USP* qs to 1 mL. The specific activity of pegaspargase is at least 85 IU per milligram protein. Available in 5 mL vials as Sterile Solution for Injection in ready to use single-use vials, preservative free. Keep refrigerated at 2°-8°C (36°-46°F). Do not use if

stored at room temperature for more than 48 hours. **DO NOT FREEZE.** Do not use product if it is known to have been frozen. Freezing destroys activity, which cannot be detected visually.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

For IM administration: the volume at a single injection site should be limited to 2 mL. If the volume to be administered is greater than 2 mL, multiple injection sites should be used.

For IV administration: dilute pegaspargase in 100 mL of NS or D5W and infuse over 1 to 2 hours through a NS or D5W running infusion line. Pegaspargase admixed in 100 mL of NS or D5W is stable for 48 hours at room temperature. Pegaspargase diluted in 100 mL of NS is stable for up to 72 hours refrigerated (4ºC [39°F]) (refrigerated stability data on file with Sigma-Tau). Avoid excessive agitation. DO NOT SHAKE. Do not use if cloudy of if precipitate is present.

Have available during and after the infusion: antihistamine, epinephrine, oxygen, and IV corticosteroids. Observe patient for ONE hour after administration for signs of hypersensitivity reactions.

6.9.4 Supplier

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

6.10 CALASPARGASE

6.10.1 Source and Pharmacology

L-asparaginase is an enzyme that catalyzes the conversion of the amino acid L-asparagine into aspartic acid and ammonia. The pharmacological effect ofCalaspargase-pegol-mknl is thought to be based on the killing of leukemic cells due to depletion of plasma asparagine. Leukemic cells with low expression of asparagine synthetase have a reduced ability to synthesize asparagine, and therefore depend on an exogenous source of asparagine for survival

Calaspargase pegol-mknl contains an asparagine specific enzyme derived from Escherichia coli, as a conjugate of L-asparaginase (L-asparagine amidohydrolase) and monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate (SC) linker. The SC linker is a chemically stable carbamate bond between the mPEG moiety and the lysine groups of L-asparaginase. L-asparaginase is a tetrameric enzyme that is produced endogenously by E. coli and consists of identical 34.5 kDa subunits. Approximately 31 to 39 molecules of SC-PEG are linked to L-asparaginase; the molecular weight of each SC-PEG molecule is about 5 kDa. The activity of ASPARLAS is expressed in units (U). ASPARLAS injection is supplied as a clear, colorless, preservative-free, isotonic sterile solution in phosphate-buffered saline, pH 7.3 that requires dilution prior to intravenous infusion. Each vial of ASPARLAS contains 3,750 units in 5 mL of solution. Each milliliter contains 750 units of calaspargase pegol-mknl; dibasic sodium phosphate, USP (5.58 mg); monobasic sodium phosphate, USP (1.20 mg); and sodium chloride, USP (8.50 mg) in water for injection, USP

Calaspargase-pegol-mknl is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years.

Pharmacology / Pharmacokinetics

Asparagine concentrations in plasma were maintained below the assay limit of quantification for more than 18 days following a single dose of calaspargase pegol 2,500 U/m2 during the induction phase. Mean CSF asparagine concentrations decreased from a pretreatment concentration of 0.8 µg/mL to 0.2 µg/mL on Day 4 and remained decreased at 0.2 µg/mL 25 days after the administration of a single dose of calaspargase pegol 2,500 U/m2 in the induction phase. Plasma asparaginase activity pharmacokinetics are nonlinear following calaspargase pegol administration. The time to peak concentration (Tmax) = 1.17 hours and Cmax = 1.62 U/mL. Area under the curve (AUC0-∞) is 25.5 day x U/mL. Calaspargase pegol has a long elimination half-life (T1/2) of 16.1 days, volume of distribution (Vss) of 2.96 L, and clearance of 0.147 L/day

6.10.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Hypersensitivity		Arrhythmia , Cardiac failure anaphylaxis
Prompt: Within 2-3 weeks, prior to the next course	Transaminitis Bilirubin increased	Pancreatitis , Abnormal coagulation studies , Albumin decreased , Fibrinogen decreased , Diarrhea , Thromboembolic events, Infection , Sepsis, Dyspnea , Hemorrhage , Antibody development	
Delayed: Any time later during therapy	Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with calaspargase pegol and for at least 3 months after the last dose. Counsel patients to use non- hormonal method(s) of contraception since calaspargase pegol can render hormonal contraceptives ineffective. There are no data on the presence of calaspargase pegol in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for adverse reactions in the breastfed child, advise women not to breastfeed during treatment with calaspargase pegol and for 3 months after the last dose		

6.10.3 Formulation and stability

Calaspargase pegol - mknl is a clear and colorless solution. Visually inspect parenteral drug products for particulate matter, cloudiness, or discoloration prior to administration. If any of these are present, discard the vial. Do not administer if calaspargase pegol - mknl has been shaken or vigorously agitated, frozen, or stored at room temperature for more than 48 hours.

Dilute calaspargase pegol - mknl in 100 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP using sterile/aseptic technique. Discard any unused portion left in a vial.
After dilution, administer immediately into a running infusion of either 0.9% sodium chloride or 5% dextrose, respectively.

Administer the dose over a period of 1-2 hours
Do not infuse other drugs through the same intravenous line during administration of calaspargase pegol - mknl.
The diluted solution may be stored for up to 4 hours at room temperature (15°C to 25°C [59°F to 77°F]) or refrigerated at 2°C to 8°C (36°F to 46°F).

Calaspargase pegol – mknl injection is supplied as a clear, colorless, preservative-free sterile solution in a single-dose vial containing 3,750 units of calaspargase pegol-mknl per 5 mL solution (NDC 72694-515-01). Store calaspargase pegol - mknl. ASPARLAS refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake or freeze product. Unopened vials may be stored at room temperature (15°C to 25°C [59°F to 77°F]) for no more than 48 hours.

6.10.4 Supplier

Servier Pharmaceuticals LLC

6.11 VINCRISTINE SULFATE (Oncovin®, VCR, LCR) NSC #67574 (11/18/11)

6.11.1 Source and Pharmacology

Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

6.11.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Jaw pain, headache	Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation	Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating
Delayed: Any time later during therapy	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop,	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders

		foot drop, abnormal gait	(including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.		

6.11.3 Formulation and Stability

Vincristine is supplied in 1 mL and 2 mL vials in which each contains vincristine sulfate, 1 mg (1.08 µmol), mannitol 100 mg, SWFI; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2˚-8˚C or 36˚-46˚F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

6.11.4 Guidelines for Administration

See Treatment and Dose Modifications sections of protocol.

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vincristine. The delivery of vincristine via either IV slow push or minibag is acceptable for COG protocols. Vincristine should **NOT** be delivered to the patient at the same time with any medications intended for central nervous system administration. Vincristine is fatal if given intrathecally.

Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vincristine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

PLEASE NOTE: The warning statement in the vincristine USP monograph has been revised as stated above to the following: "Do not remove covering until moment of injection. For intravenous use only. Fatal if given by other routes." The prescribing information for the product by Teva USA has been revised to reflect this information. At the writing of this monograph, the Hospira prescribing information had not yet been revised.

This revision can be found in Pharmacopeial Forum 36(6) which is available free of charge on the USP website at http://www.usp.org/USPNF/pf/. The notice of intent to revise can be found at the following website: http://www.usp.org/USPNF/compendialNotices/vincristineSulfate.html. The official FDA-approved labeling can be found at the NIH's DailyMed website: http://dailymed.nlm.nih.gov/dailymed/search.cfm?startswith=vincristine.

6.11.5 Supplier

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

6.12 Dexamethasone (Decadron®, Hexadrol®, Dexone®, Dexameth®) NSC#34521

6.12.1 Source and Pharmacology:

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

6.12.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	Hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitaryadrenalaxis suppression, acne *(L)*	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial,fungal, parasitic, viral), edema	Pancreatitis *(L)*, increased intraocular pressure *(L)*, hypertension, psychosis, vertigo, headache
Delayed: Any time later	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising,	Spontaneous fractures *(L)*,

during therapy, excluding the above conditions		Muscle weakness, osteopenia	growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads *(L)*
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of dexamethasone in children)	
Unknown Frequency and Timing: dexamethasone crosses the placenta with 54% metabolized by enzymes in the placenta. In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. There are no reports of dexamethasone excretion into breast milk in humans; however, it is expected due to its low molecular weight that it would partition into breast milk.			

(L) Toxicity may also occur later.

6.12.3 Formulation and Stability:

Available in 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tablets; liquid formulations are available in 0.5mg/5ml and 0.5mg/0.5ml concentration. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, and various dyes. Liquid formulations may include: 5%-30% alcohol, Benzoic acid, sorbitol, sodium saccharin, glycerin, purified water, and various dyes.

Dexamethasone sodium phosphate solution for injection is available as 4 mg/ml, 10 mg/ml, 20 mg/ml and 24 mg/ml. 4 mg of dexamethasone sodium phosphate is equivalent to 3.33 mg of dexamethasone. Vial sizes include 1 ml, 5 ml, 10 ml, 25 ml, 30 ml and are available in multidose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium citrate, sodium hydroxide to adjust pH, Water for Injection, sodium sulfite, bisulfite and metabisulfite, methyl and propyl paraben, benzyl alcohol, and EDTA.

6.12.4 Guidelines for Administration:

See Treatment and Dose Modifications section of the protocol for dose and schedule.

Dexamethasone Sodium Phosphate for Injection may be given IV, or IM undiluted. For IV use, it may be further diluted in dextrose or saline containing solutions. Avoid benzyl alcohol containing dexamethasone solutions for use in neonates. Diluted solutions that contain no

preservatives should be used within 24 hours, but maintain stability for at least 14 days in PVC bags at room temperature protected from light.

6.12.5 Supplier: Commercially available. See package insert for further information.

7.0 REQUIRED OBSERVATIONS/MATERIAL AND DATA TO BE ASSESSIONED

All protocol-specified hematology, blood chemistries, and bone marrow aspirations and/or biopsies are to be performed in the local laboratory at each investigational site.

7.1 Clinical and Laboratory Studies

All entry/eligibility studies must be performed within 1 week prior to study enrollment. Disease evaluation is required within 2 weeks prior to study enrollment. Additional assessments may be obtained as needed for good patient care.

Any Grade 3 or 4 lab tests or other adverse experiences found should be reviewed and repeated within 48 hours to determine if the grade and duration meet the definition for DLT (section 4.4)

This table represents SOC. Further tests or procedures may be needed for good clinical care.

STUDIES TO BE OBTAINED	Pre-Study	During Block 1	During Block 2	During Maintenance Block
History	X[1]	Weekly	Weekly	Monthly
Physical exam with vital signs	X[1]	Weekly	Weekly	Monthly
Height, weight, BSA	X[1]	Start of the block	Start of the block	Start of the block
Performance status	X[1]	N/A	N/A	N/A
CBC, differential, platelets Chemistry panel[2]	X[1]	Twice weekly[13]	Weekly	Start of the block
Neurological Exam[14]	X[1]	Prior to each Ixazomib dosing	Prior to each Ixazomib dosing	Perform every 28 days prior to First dose of Ixazomib
Urine pregnancy or serum β-HCG[3]	X[1]		Start of the block	Start of the block
Echocardiogram/MUGA/ECG	X[1]	End of block	End of block	Every 3 months
CSF cell count and cytospin cytology	X[1]	With each dose of IT chemotherapy	With each dose of IT chemotherapy	With each dose of IT chemotherapy
Bone marrow aspirate and/or biopsy for morphology, immunophenotyping	X[1]	Day 29-36[4] (section 4.4)	Day 29-36[4,6] (section 4.4)	X (optional)[12]
Cytogenetic analysis	X[1,11]	X (optional)[12]	X (optional)[12]	X (optional)[12]
Bone marrow for MRD[7]	X[1]	Day 29-36[4] (section 7.3)	Day 29-36[4,6] (section 7.3)	X (optional)[12]
CT and PET or gallium – lymphoma patients or leukemia patients with cholorma[5]	X[1,8]	Day 29-36[8] (section 4.4)	Day 29-36[6] (section 4.4)	X (optional)[12]
Pharmacokinetics Studies[9]	N/A	X (required)	X (required for Phase 2)	N/A

Correlative biology studies[10]	X (optional)	X (optional)	X (optional)	N/A
Palatibility studies	N/A	With each dose of ixazomib	N/A	N/A

[1]Required for verification of eligibility. FAX or email all results to the TACL Operations Center with study registration eligibility. If a patient has labs done prior to study entry that establish eligibility, then abnormal Day 1 labs do not deem them ineligible.
[2]Chemistry panel should include: chloride, sodium, potassium, magnesium, phosphorus, bicarbonate, BUN, creatinine, calcium, glucose, uric acid, total protein, albumin, total bilirubin, direct bilirubin, AST and ALT
[3]Females of childbearing potential require a negative pregnancy test prior to start treatment and must use an acceptable method of birth control. Abstinence is an acceptable methods of birth control
[4]This does not apply to lymphoma patients without marrow disease
[5]Gallium scan may be substituted for PET scan at sites where PET is not available. PET without CT should not be used as a substitute for CT with contrast at any required evaluation point. The same scanning modality (gallium or PET) should be used for all required evaluation points. Combined PET/CT is acceptable.
[6]Perform only if previous test was positive
[7]See section 7.3
[8]For lymphoma patients or leukemia patients with chloroma only
[9]Detail see section 8.3
[10]Detal see section 8.2
[11]If cytogenetics is not done at the time of pre-study evaluation, diagnostic cytogenetics is accepted.
[12] If it is performed according to standard of care, please submit data
[13]CBC twice a week are required until day 49 in the absence of hematological recovery
[14]Neurological exam should be completed using Appendix VII: Neurological Exam form

7.2 Correlative Biology Studies

Correlative biology studies include required pharmacokinetic (PK) studies and optional pharmacodynamic (PD) studies. Note: PD studies are limited to those with peripheral blasts with an absolute blast count of at least 1000 cell/uL. Unless otherwise noted, all PD studies are optional and require patient consent. For detailed information of sample collection, processing, and shipping see Section 8.0.

Studies to be obtained	Baseline (before start of chemotherapy)	Day 1 Hour 0	Day 1 Hour 6	Day 1 Hour 24
Proteasome activity	X			
Cell Stress protein assessment (RPPA)*		X	X	X
Banking**	X			

*RPPA for cell stress proteins: collect three time points if over 12kg. If under 12 kg collect 2 time points at Day 1 Hour 0 and Day 1 Hour 6 only.
**Banking: for those over 12 kg only. Please see Section 8 for volumes and tube types for sample collection.

7.3 Bone Marrow Sample for MRD

Samples requested:	**<u>Bone Marrow Sample for MRD</u>** • End of block 1 - all leukemia patients and lymphoma patients whose MRD was positive at the study entry • End of block 2 – all patients with positive MRD at end of block 1

Bone marrow Collection procedure:	a. Collect minimum of 2 mL of marrow into a syringe and place marrow into a large purple EDTA tube that are commonly used in all hospitals. Mix well. b. Use multiple syringes and tubes as needed. Reposition marrow aspirates needle at least once during procedure to ensure the maximum quality of marrow
Specimen Labeling:	Please refer to the TACL MRD Lab Manual, Section V.2 for instructions regarding specimen labeling.
Specimen Packaging and Shipping:	Please refer to the TACL MRD Lab Manual, Section V.4 for instructions regarding specimen packaging and shipping.

7.4 Palatibility Study

After each dose of ixazomib during block 1, a questionnaire will be provided to patient and parent/care giver. If the patient is too young to fill the survey, only parent/care giver will be surveyed. In each case, a nurse or research staff will record the verbal responses to the questions. When facial hedonic scales is utilized, the child or parent/care giver will be asked to indicate their preference by circling on the pictorial scale of facial expression. The palatability study questionnaire is provided in Appendix VI.

7.5 Required Observations Following Completion of Protocol Therapy

Upon completing protocol therapy or exiting the study, all patients will be followed for 2 years or until otherwise notified by the study committee that the study is closed. Sites should submit follow-up a minimum of every 6 months. Events such as patient death, relapse or development of toxicity related to this therapy should be reported right away. The purpose is to assess safety, remission status, administration of alternative therapies, and survival. The following data will be collected:

1) Disease status information
2) Anti-cancer therapy received after exiting the protocol
3) All adverse events thought to be related to this study's treatment
4) Date and cause of death

8.0 CORRELATIVE STUDIES

An important component of this study is the correlative biology studies to preliminarily assess the mechanisms of ixazomib action in vivo. Prior to proteasome and protein analysis, peripheral lymphoblasts will be separated from non-malignant white blood cells using magnetic bead sorting. The Horton laboratory has experience with the isolation and purification of leukemia cells, which was done as part of two Phase 3 COG studies.

8.1 Description of Studies

8.1.1 Studies from peripheral blood mononuclear cells (PBMCs): PK studies will be performed on plasma samples collected for this purpose (see Section 8.3). PBMCs from blood will be used for analysis of proteasome activation and protein expression profiling by reverse-phase protein microarray (RPPA). If sample is available, we will also assess protein expression for proteins regulated by the ubiquitin-proteasome pathway (UPP). Extra sample will be banked for future use. See Section 8.2 and 8.3 for test details.

8.1.2 Study Prioritization: Due to limited sample availability, sample studies will be prioritized as follows (1=highest priority, 5=lowest priority): 1. MRD assessment (bone marrow) 2. Ixazomib PK analysis (blood) 3. Characterization of proteasome activation before and after ixazomib treatment (blood) 4. Characterization of cell stress proteins by RPPA (blood) 5. Banking excess lymphoblasts and plasma for future studies (bone marrow and blood).

8.2 Sampling Schedule for optional PD studies

Peripheral blood samples should be sent to the Horton lab only if the patient samples meet the following criteria: Eligible patients must have an initial absolute blast count of at least 1000 lymphoblasts/μL. To calculate the absolute blast percentage, multiply the total WBC by the % peripheral blasts: (WBC)(% blast)(1000) = absolute blast count/μL

Sample collection volumes and time points during block 1:

	Baseline	Day 1 Hour 0 (baseline)	Day 1 Hour 6	Day 1 Hour 24
Bone marrow (induction only)[1]	3mL green top[2]			
Peripheral blood (induction only)[3]	5mL in heparin for proteasome assessment[4]	3mL in Cellsave[5] 2mL in heparin[4]	3mL in Cellsave[5] 2mL in heparin[4] (4-6h after start of systemic chemo)	3mL in Cellsave[5] 2mL in heparin[4] (24h after the start of systemic chemotherapy)

[1]Only applies to patients ≥ 12 Kg
[2]Peripheral blood (20mL) with >80% blasts can be substituted if bone marrow not obtained.
[3]Modified blood volumes for those under 12 kg (see 8.2.1 and 8.2.2 below)
[4]Before the start of systemic chemotherapy. Can be collected after IT chemotherapy
[5]Cell Save preservation tubes will be provided by the Horton lab on study activation. Replacement tubes will be provided once the first set us utilized. Call the Horton lab for replacement tubes. If Cell Save tubes are not available, collect 5cc in heparin tubes.

8.2.1 Patients ≥12 kg: On study: Five mL blood sample obtained prior to beginning Block 1 treatment on the same day as the pretreatment bone marrow aspirate (3ml). Block 1, Day 1: Five mL total blood sample at 3 time points: prior to start of chemotherapy, at 4-6 hours and 24 hours following the first ixazomib dose

8.2.2 Patients under 12 kg: On study: Three mL blood sample obtained prior to beginning Block 1 treatment. No pretreatment bone marrow aspirate is needed. Block 1, Day 1: Three mL blood sample drawn at 2 time points: prior to start of chemotherapy and 4-6 hours after the first ixazomib dose.

8.2.3 If possible, do not perform end of block bone marrow aspirate on a Friday to avoid sample shipment on the weekend. This means the “Day 36” sample may actually be collected on Day 34-37.

8.3 Blood for PK Analysis (mandatory)

Blood samples will be collected from all subjects enrolled in phase 1 for determination of plasma concentrations of ixazomib. Sparse PK sampling will be used in patients enrolled in the phase 2

study. The PK sampling schedule is provided in the tables below. The exact date and time of each ixazomib dose, and each PK sample collection will be recorded.

PK parameters for ixazomib will be calculated as appropriate from the ixazomib plasma concentration-time data. PK parameters will be summarized using descriptive statistics. The PK data collected in these studies will contribute to population PK analyses of ixazomib and may also be used to examine the exposure-efficacy and exposure-safety relationships for ixazomib.

Phase 1, PO dosing

Weight	Block 1 Day 1	Block 1 Day 11	Volume/30 days
<20 kg	72 h post-dose (to be collected prior to the Block 1 Day 4 dose of ixazomib)	Pre-dose, 30 min, 4 h, 72 h post-dose	10 mL
≥20 kg	30 min, 1 h, 2 h, 4 h, 8 h, 24 h, 72 h post-dose (the 72 h sample is to be collected prior to the Block 1 Day 4 dose of ixazomib)	Pre-dose, 30 min, 1 h, 2 h, 4 h, 8 h, 24 h, 72 h, 264 h post-dose	32 mL

Phase 2, PO dosing

Weight	Block 1 Day 1	Block 1 Day 8	Block 1 Day 11	Block 2 Day 1	Block 2 Day 15	Block 2 Day 18	Volume/30 days
<20 kg	72 h post-dose (to be collected prior to the Block 1 Day 4 dose of ixazomib)	Pre-dose	Pre-dose, 72 h post-dose (Block 1 Day 14)	-	-	-	8 mL
≥20 kg	72 h post-dose (to be collected prior to the Block 1 Day 4 dose of ixazomib)	Pre-dose	Pre-dose, 30 min, 2 h, 4 h, 72 h post-dose (Block 1 Day 14)	Pre-dose	Pre-dose	Pre-dose	20 mL

Samples requested:	Blood samples for PK studies
Blood Collection procedure:	2 mL PK samples should be collected into tubes provided in the ixazomib PK collection kit. This will be provided by Takeda Pharmaceuticals. **Materials** Blood samples for PK assessment must be collected in 2-mL vacutainer tubes containing K_2EDTA as the anticoagulant. Resulting blood and plasma PK samples must be stored in plastic storage tubes with caps. No blood collection tubes with separation gel should be used. Plasma (0.5 mL) is stored in tubes containing 250 mg lyophilized citric acid.

	Preparation of Plasma Pharmacokinetic Samples 1. Draw blood into labeled and chilled 2-mL lavender top K_2EDTA vacutainer tube. 2. Mix the blood with the anticoagulant by gently inverting the tube 8-10 times and immediately place on wet ice. 3. Centrifuge the blood samples for 10 minutes at 1000 x g at 4º C in a refrigerated centrifuge within 10 minutes of sample collection. 4. Immediately following centrifugation, gently remove the plasma from the packed cells and aliquot into transfer vials filled with lyophilized citric acid. **Each aliquot should contain exactly 0.5 mL of plasma**. 5. Vortex split tubes thoroughly. Any remaining plasma post-split 1/split 2 sample aliquots should be discarded following appropriate biohazard disposal procedures. NOTE: If < 0.5 mL plasma is obtained post centrifugation, do not process or store split 1 or split 2, record split 1: ISV (Insufficient Sample Volume), split 2: ISV**. If < 1.0 mL plasma is obtained post centrifugation, process and store split 1 according to procedure; do not process or store split 2, record split 2: ISV.** Discard remaining plasma using appropriate biohazard waste disposal procedures. 6. Replace cap on tube and freeze the samples immediately at -70°C. Note: No more than 60 minutes should elapse between blood collection and freezing the plasma samples. 7. Keep samples frozen at -70°C or lower until shipment. Note: Wet ice is defined as a mixture of ice and water.
Specimen Labeling:	Each tube must be labeled with the study ID number, along with the date and time of when the sample was obtained. No personal identifying patient information should be included in the specimen or transmittal form.
Specimen Packaging and Shipping:	Covance Clinical Laboratory Services 8211 Scicor Drive, Indianapolis, IN 46214 USA

Document the exact dates and times of ixazomib administration and sample collection on the Pharmacokinetics Study Form (Appendix III) and in the eCRF. Ensure that any information requested on the tube label is completely filled out and legible**.**

8.4 Additional Information for Correlative Studies

The following correlative studies will be performed on patients with ALL who consent to participate. Peripheral blood samples will be collected prior to the start of treatment (Proteasome assay) and on Day

1 of treatment at hour 0, at 4-6 hours, and 24 hours (in patients ≥ 12 kg) following the first dose of ixazomib (Protein microarray).

8.4.1 Proteasome activity
The activity of the 26S constitutive and immunoproteasome subunits (β5, iβ5, β1 and iβ1) will be performed on peripheral blood for patients with at least 1000 cell/uL absolute blast count. Work will be done through the Horton laboratory in collaboration with Jaqueline Cloos, VU Medical Center, Amsterdam, the Netherlands.

8.4.2 Protein microarray:
Protein expression in malignant lymphoblasts will be analyzed using capillary electropheresis and/or reverse-phase protein lysate arrays in Dr. Horton's laboratory. RPPA analysis will have higher priority since many more proteins can be assessed using small amounts of material (200,000 cells). RPPA will be performed as previously described.[55] Capillary electrophoresis will be performed according to the manufacturer's directions using commercially available antibodies. The investigators (Horton and Kornblau labs) have extensive experience with their respective techniques.[56]

8.4.3 Banking:
Peripheral blood samples remaining after RPPA and immunoblot will be banked for future proteomic studies. If the patient consents to banking, any excess lymphoblasts, non-malignant lymphocytes and plasma leftover from research tests will be banked for future TACL biology studies and stored within the TACL Central Biological Repository under the TACL T2016-005 study. Samples will remain linked to their TACL identification number.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY, OFF STUDY CRITERIA AND STUDY TERMINATION

9.1 Criteria for Removal from Protocol Therapy

Response evaluable patients will be followed for a duration of a minimum of four months and maximum 2 years; toxicity evaluable but not response evaluable patients will be followed for one month after discontinuation of study therapy.

a. Patient is not CNS 1 or 2 after the first course of therapy (this excludes patients who are CNS 3 due to chloromas or cranial nerve involvement with evidence of improvement).
b. Relapse in any site following remission
c. Progressive disease
d. Completion of protocol therapy
e. Second malignant neoplasm
f. Patient/parent withdrawal or refusal after beginning protocol therapy
g. Patient off treatment for other complicating disease
h. Non-compliance with protocol regimen and procedures
i. Investigator determination
j. Female patient becomes pregnant or begins breast-feeding

9.2 Off Study Criteria

a. Death
b. Patient Lost to follow-up
c. Patient withdraws consent, refuses follow-up

9.3 Termination of the Study by TACL

The TACL Consortium may terminate this study prematurely, either in its entirety or at an investigative site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns.

10.0 STATISTICAL CONSIDERATIONS

10.1 Design Overview

This is a Phase 1/2 study that comprises two strata.

- Stratum A (primary) includes all eligible patients who are ≥ 1 year of age and who do not have Down syndrome (DS).
- Stratum B (secondary) includes all eligible patients who are either < 1 year of age or who have DS.

The primary dose finding (Phase 1) and response evaluation expansion (Phase 2) will occur in Stratum A. A modified dose escalation, as described below, will occur in Stratum B. Down syndrome patients enrolled in Stratum B will receive 1.6 mg/m^2 in Phase 2, which is one dose level below for the non-DS patients.

10.1.1 **Phase 1**

The phase 1 portion is a 3+3 dose escalation study to determine the MTD/RP2D of PO ixazomib in combination with VXLD therapy. This design targets DLT rates on the order of 15-20%, which is considered acceptable for this regimen.

Enrollments are planned in groups of up to three patients, with doses escalated or de-escalated according to the rules of the 3+3 dose-escalation design, as follows:

- Up to 3 patients are entered at the starting dose level
- If 0 of 3 patients experiences DLT at a given dose level, then the dose is escalated to the next higher level, if a higher dose level exists, and up to three patients are enrolled. If a higher dose level does not exist, up to three additional patients are accrued at the same dose level.
- If 1 of 3 patients experiences DLT at current dose, then up to three additional patients are accrued at the same dose level.
- If 2 or more DLTs are observed at a given dose level, then the MTD has been exceeded, dose escalation and accrual to the current dose level will be stopped, and up to three additional patients will be enrolled at the next lower dose level, if a lower dose level exists, unless six patients have already been treated at that lower dose.

The MTD is the highest dose level tested at which 0/6 or 1/6 patients experience DLT with at least two patients encountering DLT at the next higher dose. If the highest specified dose level is reached with 0/6 or 1/6 patients experiencing DLT, i.e., the MTD has not been reached, this dose level will be referred to as the Highest Tested Dose (HTD). The MTD or HTD will be the recommended Phase 2 dose (RP2D). If at least two patients encountering DLT at the lowest dose, then no MTD exists.

For Stratum A patients, the starting dose will be 1.6mg/m^2/day (see Section 4.5). Escalation/de-escalation decisions will be based on the DLTs that occur during the first block of treatment.

Stratum B patients will not be included in the primary DLT or response evaluation due to their unique biology and toxicity profile. To ensure the safety of these patients, they will be entered at

one dose level below a determined safe dose level in older children (which is defined as a dose at which 0/3 or ≤ 1/6 patients have experienced a DLT), and will follow a 3+3 dose escalation design for safety, although there is no expectation that this dose escalation will be completed. At no time will the dose given to infants or Down syndrome patient exceed the currently established safe dose in non-infant/non-Down patients.

Accrual: In Stratum A, the phase 1 portion will require a minimum of 4 and maximum of 18 DLT evaluable. Likely accrual is 9-12 DLT evaluable patients if an RP2D is determined, requiring 12-18 months. A small number of additional patients will be enrolled in Stratum B.

During Phase 1, enrollment will be restricted initially to patients < 18 years of age until a minumum of 9 such patients have been enrolled.

10.1.2 Phase 2

If an RP2D is established for Stratum A, a phase 2 expansion will be performed at the RP2D in Stratum A and one dose below the RP2D in patients with Down syndrome or less than 1 year of age. Stratum A patients satisfying the phase 2 eligibility criteria will be enrolled and treated at the RP2D until 18 response evaluable patients have been treated at the RP2D or until a total of 24 evaluable patients (including both phase 1 and 2 enrollments) are enrolled, whichever occurs first. Response-evaluable Stratum A patients treated at the PO RP2D in phase 1 will be included in the phase 2 analysis and be counted toward the 18 response evaluable patients.

Interim analysis. There will be no interim analyses for futility or efficacy during phase 2.

Accrual. A minimum of 6 and a maximum of 12 response evaluable patients will be enrolled in Stratum A during the phase 2 expansion, for a total of 12-18 response evaluable patients accrued for analysis. Stratum B patients with Down syndrome or less than 1 year of age can be enrolled, but will not be counted toward the target accrual and not included in the primary response analysis. During the phase 2 expansion, Stratrum A enrollment will be restricted initially to patients < 18 years of age until a minumum total of 6 such patients have been enrolled at the RP2D. The estimated time to complete phase 2 accrual is 12-18 months. Assuming a maximum non-evaluability rate of 10%, a maximum of 26-27 patients in Stratum A will be required to complete both phase 1 and phase 2.

10.2 Endpoints

Primary Endpoints:

- Phase 1: Dose limiting toxicity (DLT) during block 1 of chemotherapy
- Phase 1: PK parameters of ixazomib during block 1 of chemotherapy
- Phase 1: CTCAE toxicities during block 1 of chemotherapy
- Phase 2: Response (CR+ CR MRD-, and CR + CR MRD- + CRi) after block 1 chemotherapy

Secondary Endpoint:

- CTCAE toxicities during block 2 chemotherapy
- Palatibility study of ixazomib

Exploratory Endpoints:

- Proteasome activity and cell stress protein in peripheral blasts.
- CTCAE toxicities during maintenance therapy

- Response (CR+ CR MRD-, and CR + CR MRD- + CRi) after block 2 re-induction chemotherapy
- Event-free survival (EFS), defined as the time from study entry to the earliest occurrence of failure to respond to block 1 of treatment, disease progress, disease relapse, or death from any cause.
- Overall survival (OS), defined as the time from study entry to death from any cause.
- MRD status after block 1 and block 2 therapy

10.3 Patient Evaluability and DLT Definition

10.3.1 Definition of a patient evaluable for dose limiting toxicity (DLT)

Patients are evaluable for DLT if, during the first block of therapy, they receive at least one dose of Ixazomib and they terminate treatment for toxicity or intolerability, they experience a DLT, or they receive at least 75% of the required dose of ixazomib without DLT. The required dose of Ixazomib is defined as the total nominal dose during the block per sections 4.1, 4.2, or 4.3, adjusted for any dose modifications due to renal or hepatic impairment as per sections 4.7.1.2 and 4.7.1.3. During phase 1, patients who do not satisfy one of these conditions are not evaluable for toxicity and will be replaced

10.3.2 Definition of a patient evaluable for response

A patient will be considered evaluable for response if the patient receives all or part of protocol therapy and the patient is under follow-up for a sufficient period to evaluate the disease at the end of the block 1. A patient will also be considered evaluable for response if the patient meets the definition of progressive disease or dies as the result of a DLT. A patient who dies as a result of a DLT after receiving all or part of protocol therapy will be considered a non-responder. Patients who are not considered evaluable for response will be replaced.

10.4 Interim Monitoring of Toxic Death

The occurrence of toxic death (TD, defined as treatment related mortality) at any time during protocol therapy, or until 30 days following the last dose of study therapy, will be a primary endpoint for safety monitoring. A population toxic death rate that exceeds p0=0.10 will be considered unacceptable. A Bayesian monitoring rule based on a pessimistic Beta (1,3) prior distribution on the parameter p0 will be used to judge the evidence that the population toxic death rate exceeds this quantity. This prior has mean 0.25, median 0.21, and 90% of support under 0.54. A posterior probability of greater than 80% that p0>0.10 will be considered statistical evidence that the population toxic death rates may exceed 0.10. Operationally, this criterion will be satisfied if the following fractions of TDs out of total patients treated are exceeded: ≥1/5, ≥2/12, ≥3/20, ≥4/28, and so on as dictated by this rule. If this criterion is satisfied at any time the cause and circumstances of these deaths will be reviewed with the study committee and with the Data and Safety Monitoring Committee to determine whether modifications to or termination of the study is warranted.

10.5 Analysis of primary and secondary endpoints

Analysis of DLT. Analysis of DLT will be in the context of the dose escalation design described above.

Analysis of Toxicity. CTCAE grade 3+ hematologic and non-hematologic toxicities, overall and attributable to ixazomib, will be summarized as percents of patients experiencing these toxicities, with associated standard errors, for each treatment block and for the entire treatment course.

Analysis of Response. The analysis of the phase 2 portion will focus on estimating the response rate following block 1 of treatment. With a maximum sample size of 18 response evaluable patients, the standard error (SE) of the overall estimate of response rate will be at most 0.12,. The minimum sample size of 12 response evaluable patients corresponds to a SE of at most 0.14.

Analysis of PK. For patients enrolled in the phase 1 portion, PK parameters will be summarized descriptively as permitted by the data.. If sample size permits, the relationship between ixazomib dose and ixazomib PK parameters may be examined to assess dose linearity.

The PK data collected in the phase 1 and phase 2 portions will contribute to population PK analyses of ixazomib and may also be used to examine the exposure-efficacy and exposure-safety relationships for ixazomib. These analyses will be reported separately.

10.6 Analysis of exploratory endpoints

The analysis of ixazomib PD, post block 1 and block 2 MRD, and other exploratory endpoints will be primarily descriptive, but will comprise at minimum summarizing these difference measures as means, proportions, or in the case of EFS and OS, the 4-month and two-year EFS and OS probability as estimated via the product limit estimator, with associated standard errors.

10.7 Inclusion of Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. The small number of patients entered into this trial will obviate any analysis of variation in response rate with gender or ethnicity.

11.0 RESPONSE CRITERIA

11.1 Bone Marrow Response Criteria for patients with leukemia

11.1.1 **Complete Remission (CR)**

- A bone marrow with <5% blasts by morphology; and
- No evidence of circulating blasts or extramedullary disease; and
- Recovery of peripheral counts (ANC ≥ 500/μL and PLT count ≥ 20,000/μL, platelet infusion independent).

11.1.2 **Complete Remission, MRD negative (CR MRD-)**

- A bone marrow with <5% blasts by morphology; and
- MRD <0.1% by flow or molecular testing (e.g. PCR); and
- No evidence of circulating blasts or extramedullary disease; and
- Recovery of peripheral counts (ANC ≥ 500/μL and PLT count ≥ 20,000/μL, platelet infusion independent).
- Qualifying marrow and peripheral counts should be performed within 1 week of each other

11.1.3 **Complete Response with Incomplete Count Recovery (CRi)**

- A bone marrow with <5% blasts by morphology; and
- No evidence of circulating blasts or extramedullary disease; and

- Insufficient recovery of absolute neutrophil counts (ANC <500/µL), and/or insufficient recovery of platelets (PLT counts <20,000/µL, platelet infusion independent),

11.1.4 **Partial Response (PR)**

- Complete disappearance of circulating blasts and one of the following:
- A decease of at least 50% of blasts in the bone marrow with ≥5% and ≤ 25% blasts by morphology with recovery of peripheral counts (ANC ≥ 500/µL and PLT count ≥ 20,000/µL, platelet infusion independent)
  Note: only patients who entered the study with ≥ 25% blasts in the marrow may be assessed as PR
- Attainment of a bone marrow CR (<5% blasts by morphology) with proven persistence of extramedullary disease qualifies as a PR

11.1.5 **Stable Disease (SD)**

Patient does not satisfy the criterion for either CR, CR MRD-, CRi, PR or disease progression.

11.1.6 **Progressive Disease (PD)**

An increase of at least 25% (with a minimum increase of of 5000 cell/µL) in the absolute number of bone marrow or circulating leukemic cells, development of new sites of extramedullary disease, or other laboratory or clinical evidence of progression of disease.

11.1.7 **Non-responder (NR)**

A patient who dies from a DLT will be considered as a non-responder, regardless of the disease assessment.

11.1.8 **Not evaluable (NE)**

Aplastic or severely hypoplastic marrow with any blast percentage. Bone marrow aplasia/hypoplasia is defined as overall marrow cellularity less than 10-20%. In this instance, marrow evaluation should be repeated every 1-2 weeks until response determination can be made or patient meets criteria for a DLT of prolonged myelosuppression (as defined in section 4.4).

11.1.9 **Relapse**

After documentation of remission, one bone marrow aspirate and/or biopsy showing ≥5% leukemic blasts or pathological evidence of extramedullary disease.

11.2 CNS Response Criteria

11.2.1 CNS Status Definitions for Patients with ALL

CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of white blood cells (WBCs).

CNS 2: In CSF, presence < 5/µL WBCs and cytospin positive for blasts, or ≥ 5 /µL WBCs but negative by Steinherz/Bleyer algorithm:
CNS 2a: < 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts;
CNS 2b: ≥ 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts; and
CNS 2c: ≥ 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (formula below).

CNS 3: In CSF, presence of ≥ 5/μL WBCs and cytospin positive for blasts **and/or** clinical signs of CNS leukemia:
CNS 3a: < 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts;
CNS 3b: ≥ 10/μL RBCs, ≥ 5/μL WBCs and positive by Steinherz/Bleyer algorithm (formula below).
CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

11.2.2 Method of Evaluating Initial Traumatic Lumbar Punctures:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/μL and blasts, the following Steinherz/Bleyer algorithm should be used

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis.

Example: CSF WBC = 60/μL; CSF RBC = 1500/μL; blood WBC = 46000/μL; blood RBC = 3 X 10^6/μL:
60/1500 **= 0.04 > 2X** 4600/3x10^6 **= 0.015**

Therefore this patient has CNS disease because 0.04 > 2X 0.015

11.3 Response Criteria for Patients with Lymphoma

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[57] Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

11.3.1 Definitions

Evaluable for objective response:

Patients who exhibit objective disease progression prior to the end of block 1 will be considered evaluable for response. For all other patients, only those patients who have measurable disease present at baseline, have received at least one block of therapy, and have had their disease re-evaluated will be considered evaluable for response.

Evaluable Non-Target Disease Response:

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one block of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.3.2 Disease Parameters

Measurable disease:

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes:

To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.3.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or

calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A ‘positive’ FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.3.4 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm..

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

11.3.5 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Overall Best Response Assessment: Each patient will be classified according to his “best response” for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 11.5 from a sequence of overall response assessments.

11.3.6 Response Criteria for Patients with Lymphoma and Evaluable (but not Measurable) Disease

Evaluable Disease: The presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.
Complete Response: Disappearance of all evaluable disease.
Partial Response: Partial responses cannot be determined in patients with evaluable disease
Stable Disease: That which does not qualify as Complete Response (CR), or Progressive Disease.
Progressive Disease: The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.
Overall Best Response Assessment: Each patient will be classified according to his “best response” for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 11.5 from a sequence of overall response assessments.

11.3.7 Best Response

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest

measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 3: For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥28 days Confirmation**
CR	Non-CR/Non-PD	No	PR	≥28 days Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥28 days from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 4: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Table 5. Sequences of overall response assessments with corresponding best response.

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Definitions

Adverse Event: An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction (SAR): Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not available, is not consistent with the risk information described in the general investigational plan.

Serious Adverse Events (SAE) or Serious Suspected Adverse Reactions (SSAR): An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that results in fetal loss.

Persistent or Significant Disability/ Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (*e.g.,* sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

12.2 Data Collection

Adverse events and suspected adverse reactions (CTCAE v5.0 grades 1-5) will be collected and reported on the electronic CRFs beginning with the first dose of study therapy until 30 days following the last dose of study therapy. The investigator will evaluate all adverse events and suspected adverse reactions as to their severity and relationship to ixazomib as well as the regimen as a whole. **Serious adverse events and suspected adverse reactions will require expedited reporting to the TACL Operations Center as described below.**

12.3 Reporting Serious Adverse Events or Serious Suspected Adverse Reactions

12.3.1 The following serious adverse events or serious suspected adverse reactions requires expedited reporting:

All Grade 5 events regardless of causality.

All Grade 4 & 3 events unexpected & expected that are possibly, probably or definitely related to ixazomib or the regimen as a whole. Exclude reporting of hematologic toxicity as a serious adverse event unless the event meets the criteria of hematologic dose limiting toxicity per protocol section 4.6: Bone marrow aplasia: > 49 days from Day 1 of therapy will be a DLT. Aplasia is defined as the failure to recover a peripheral ANC of ≥ 500/μL and PLT ≥ 20,000/μL in the absence of persistent leukemia.

12.3.2 Steps for Reporting

Step 1: Identify the adverse event or suspected adverse reaction using the NCI Common Toxicity Criteria (CTC), version 5.0.

The CTC provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTC can be downloaded at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf#search=%22CTCAE%22.

Step 2: Grade the event using the NCI CTCAE version 5.0.

Step 3: Determine if the adverse event or suspected adverse reaction meets the criteria of being "serious".

Step 4: Determine the relationship of DRUG and the regimen as a whole to the event
The investigator will assess the causal relationship between the investigational product and the regimen as a whole and the adverse event. The investigator will use his/her clinical expertise and judgment to select the attribution category below that best fits the circumstances of the AE.

Unrelated: The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.

Unlikely: The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

Possible: The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.

Probable: The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

Definite: The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

Step 5: Determine if the adverse event or suspected adverse reaction is "unexpected".

Step 6: Notify the TACL Operations Center by email

The following information should be submitted **within 24 hours** of event notification by email tacl@chla.usc.edu.

1. Patient TACL study ID and initials
2. Event description
3. Severity (NCI Grade)
4. Onset date
5. Reason event is considered serious
6. Dose of study drug and dates of administration
7. Investigator opinion of relationship to DRUG and the regimen as a whole
8. Name and phone number of physician in charge of the case
9. Name and phone number of CRA or Research nurse working with the case

Step 7: Submit a written report to the TACL Operations Center

Complete the TACL SAE Notification Form within 72 hours of learning of the event. The completed form is email to tacl@chla.usc.edu. The form may also be faxed to (323) 361-4505. A follow-up SAE

Notification Form must be submitted upon resolution of the event. Please confirm via email or phone that the TACL Operations Center has received this notification.

Step 8: TACL Operations to provide notification to Takeda

Upon review of notification and outcome of SAE by TACL Study Chair/Vice Chair, submission of documents will be provided toTakeda.

12.4 Institutional Reporting to the IRB

All SAE's should be reported to the treating institutions IRB or Ethics board. The TACL Operations Center will also report all SAE's to the CHLA IRB. The TACL Operations Center will distribute SAE's to all TACL sites as appropriate for submission to their own IRB's.

13.0 DATA AND SAFETY MONITORING

13.1 Data Submission

All study data will be submitted via electronic data capture forms using the iMedidata/TACL Website. Please refer to the TACL web site (https://tacl.chla.usc.edu) for Medidata user manual or contact the TACL Operations Center at (323) 361-5132 if you need assistance.

The following are required to be submitted to the Operations Center for all patients entered:
Paper copy of following**:** Roadmaps and Bone Marrow Reports (include both aspirate and biopsy reports). These forms are to be e-mailed (tacl@chla.usc.edu) or faxed to the TACL Operations Office at (323) 361-4505 at the end of each course during which the bone marrows are done.

13.2 Weekly Safety Review

The TACL Operations Center (TOC) conducts weekly (as needed) patient safety and review meetings with the protocol chair, protocol vice-chair, research coordinators and other administrative TACL team members to review all data submitted, non-serious adverse events and other correspondence pertaining to patients. Serious adverse events will be immediately evaluated by the study team and determination regarding notification of participating sites will be made. All serious adverse events will be sent to the CHLA CCI and DSMC if required. Any interim results that would affect patient safety would be immediately communicated to all participating TACL sites. All correspondence with sites will be done via email, with all information also being posted on a member's only section of the TACL website.

13.3 Data Safety and Monitory Committee

DSMC meetings will occur every 6 months. Every 6 months, a DSMC report for each protocol will be prepared by the study statistician and study PI detailing patient accrual, toxicities, deaths on study, current study status, responses (responses will be blinded until study completes accrual), summary of amendments to protocol/consent, lists of any publications from study, and plans for study in coming year. Any publications from the study (abstract or manuscript) will be attached to the DSMC report. After DSMC review, the DSMC will issue a confidential report for each study to the study PI and TACL Operations Center.

Not more than 8 weeks after the DSMC meeting, a DSMC public review report will also be created for each protocol after approval of the confidential report and resolution of any issues by the PI The public report will then be emailed to the participating sites for each study. These can be filed at the IRB at each site if required per local IRB guidelines.

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Local IRB changes to this document are allowed. Changes within the document should not substantially alter the meaning or intent of the consent document. If the institution or IRB insists on making deletions or more substantive modifications to the consent, especially in the risks sections, they should be reviewed and approved by the TACL Operations Center.

15.0 SAMPLE INFORMED CONSENT

SAMPLE INFORMED ASSENT*/CONSENT DOCUMENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

***Assent for patients >14 years of age**

***Assent for patients <14 years of age should be written per institutional guidelines**

TACL Protocol

A TACL Phase 1/2 Study of PO Ixazomib in Combination with Chemotherapy for Childhood Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

Subject Name:	
Medical Record #	
Physician:	

KEY INFORMATION

(1) The information in this form is being used to seek your consent for a research study. Participation in the study is completely voluntary.

(2) This research is being done to find the optimal dose of Ixazomib with intensive chemotherapy and to know the side effects (good/bad) that it may cause. Participation will last up to 24 months. Study procedures for this research are:

- Take a study drug, Ixazomib, on various days by mouth along with other chemotherapy drugs that will be given to you by various methods (such as injections).
- Allow to collect blood samples from you by inserting a needle into a vein or by using your peripheral or central line.
- Complete a questionnaire about the smell and taste of the study drug.
- Participate in optional biology studies allowing us to collect additional bone marrow and blood specimens and storing those leftover specimens for use in future research studies.
- Allow the research team to review and record information from your medical record.

(3) The most likely risks to you of the research are:

- Chemotherapy side effects, such as feeling tired, anemia, and easily bruised, loss of appetite, shortness of breath, headaches, or nerve pain, or allergic reactions.

Please see the **POTENTIAL RISKS AND DISCOMFORTS** section for a complete list of expected risks.

(4) The most likely benefits to you of the research are: Researchers believe this therapy may stop your leukemia or lymphoma to stop growing or go into remission for a period of time.

(5) If you decide to not be in the research, your choices are:

- Receive other combinations of chemotherapy
- Decide not to receive additional chemotherapy for your condition.

When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

This study is being carried out by the Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Consortium. TACL is a group of Universities and Children's Hospitals that are working together to find treatments for children with leukemia and lymphoma. Funding for this research is provided by Takeda Pharmaceuticals Company Limited, or its affiliates (Takeda).

You are being asked to take part in this research study because your ALL or Lymphoblastic Lymphoma (LLy) has come back (relapsed) or didn't respond to the standard therapy.

This is a phase 1/2 study of a drug called Ixazomib in combination with cytotoxic chemotherapy consisting of Vincristine, Dexamethasone, Asparaginase, and Doxorubicin (VXLD) during Blocks 1, 2, and Maintenance phase. Ixazomib is considered experimental because it has not been proven to work in a situation like yours. It is a drug given orally. Ixazomib taken with lenalidomide and dexamethasone is approved by the Federal Drug Administration for the treatment of patients with multiple myeloma who have received at least one prior treatment for their multiple myeloma. It is not known if ixazomib is safe and effective in children. We are studying whether adding ixazomib to the chemotherapy we routinely used to treat your cancer can increase response to the therapy. This is called a Phase 1/2 study because the goal is to find the optimal dose of Ixazomib that we can give safely in combination with intensive chemotherapy, and whether this combination could improve the response rate of the chemotherapy.

It is important for you to know why this study is being done before you decide to take part in this research study. This consent will tell you about the study. This consent will also tell you about risks and side effects that might happen to you if you take part in this study. You also need to know you do not have to take part in this study. You can talk to your doctor about other cancer treatments. Because all of the drugs used in this study are each available to doctors, it is possible for you to receive these drugs without taking part in this study. Taking part in this study is voluntary.

Why is this study being done?

We are testing new experimental drug combinations such as the combination of Ixazomib with cytotoxic chemotherapy consisting of Vincristine, Dexamethasone, Asparaginase, and Doxorubicin (VXLD) during Blocks 1, 2, and Maintenance phase in the hopes of finding a drug combination that may be effective against relapsed leukemia and lymphoma.

The goals of this study are:

- To find the optimal dose of Ixazomib that can be given with intensive chemotherapy without causing severe side effects;
- To learn what kind of side effects Ixazomib can cause;
- To learn more about the pharmacology (how your body handles the drug) of Ixazomib;
- To learn how Ixazomib affects specific molecules on leukemia and lymphoma cells;

To determine whether Ixazomib, combined with intensive chemotherapy is a beneficial treatment for your ALL or LLy.

How many people will take part in this study?

It is expected that approximately 27 children and young adults will take part in this study.

What will happen if I take part in this research study?

Before you begin the study…

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of your regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. The results of these tests will be reviewed. It is possible that after these tests are reviewed, you will not be able to take part in the study. If you are not able to take part in the study, your doctor will discuss with you the reasons why.

- A medical history
- Physical exam with vital signs
- Bone marrow test to check your cancer (see Tests on the Bone Marrow, below)
- Lumbar puncture to test the fluid in your spinal cord (see Lumbar Punctures, below)
- Various blood tests to check your organ function
- Tests to make sure you are not pregnant (if you are a female and old enough to become pregnant)
- Echocardiogram (ECHO) which uses sound waves to test heart function
- CT / PET or Gallium Scans to check your cancer (for some patients)
- Neurological exam

Tests on the Bone Marrow

Examinations of the bone marrow will be performed routinely and may be done at the discretion of your study doctor. You have already had many tests of your bone marrow for your previous treatment of ALL or LLy. Many children receive some form of sedation or anesthesia during this procedure. A small area over your hip bone on the back will be cleaned and numbed with lidocaine and/or with an anesthetic cream. Approximately a little less than 3 teaspoons of bone marrow will be withdrawn through a needle inserted into the bone. The test is painful, especially when the bone marrow is withdrawn. There is also a small risk of bleeding or infection from this procedure.

Lumbar Punctures (“L.P.s”, “spinal taps”)

You are familiar with spinal taps since they were done during your initial therapy for leukemia or lymphoma ALL or LLy. Whether you decide to participate or not in this study, spinal taps will need to be done to give medicines, which are necessary to prevent the leukemia from spreading to the spinal fluid. Participating on the study doesn’t require additional spinal taps. Your doctor will decide what medication(s) to be injected into your spine while you are having a lumbar puncture. This way of giving medicine is called “intrathecal” or IT. Many children receive some form of sedation or anesthesia during this procedure. Spinal taps are painful and may cause headaches. The skin at the site of needle insertion is usually numbed with an anesthetic cream or lidocaine before the procedure is performed. Approximately a little less than a teaspoon of spinal fluid will be withdrawn prior to injection of the medicine.

During the study…

If the exams, tests and procedures show that it is safe for you to be enrolled on the study you will receive treatment courses detail below.

Various methods will be used to give drugs:

- IV – Drug is given using a needle or tubing inserted into a vein, It can be given by IV push over several minutes or by infusion over minutes to hours
- PO-Drug is given by capsule or liquid swallowed through the mouth
- IM- Drug is given using a needle for single injection into the muscle.
- IT – Drug used to treat the brain and spinal cord is given using a needle inserted into the spinal canal

Block 1 will consist of the following medications: Ixazomib by mouth on days 1, 4, 8, and 11. Vincristine will be given by intravenous (IV) infusion on days 1, 8, 15, and 22. Dexamethasone will be given by intravenous (IV) infusion or by mouth on days 1 – 14. Pegaspargase will be given by IV injection on day 2 and 15. Doxorubicin will be given via IV on day 1. You will then recover from the combined therapy. After block 1 therapy, based on your response, your doctor will discuss with you about the options of moving onto block 2 therapy, going directly to maintenance therapy up to 4 cycles, and/or going off protocol therapy.

We highly recommend you remain in the hospital during the block 1 from the time you start the therapy (or from Day 1) until blood work and your medical team determine it is safe for you to be sent home. It will be mandatory that you are started on preventative antibiotics and anti-fungal while you are hospitalized.

Treatment

Block 1

Days	1	2	4	8	9	11	14	15	16	18	22	23	29	30
Ixazomib*	●		●	●		●								
Vincristine IV (1.5mg/m^2)	●			●				●			●			
Dexamethasone IV/PO (10mg/m^2)	→	→	→	→	→	→	→							
Pegaspargase IV/ IM (2500 IU/m^2) √ ±		●						●					BM	
OR Calaspargase IV (2500 IU/m^2) √ ±		●												
Doxorubicin (60mg/m^2)	●													
Initial IT chemotherapy	●													
CNS 1/2: IT Methotrexate								●					●‡	
CNS 3: IT Triple				●				●			●		●‡	
Leucovorin IV/PO (5 mg/m^2 at hr 24 and 30 post-ITs)^		●			●				●			●		●

‡ IT therapy assigned to be given on Day 29 may be moved such that it may be given at the time of the end of Block 1 bone marrow/disease evaluation.

√ Either Pegaspargase OR Calaspargase will be administered according to current approved labeling based on age and regional availability. Patients who start on either Pegaspargase or Calaspargase must continue the same treatment throughout the treatment cycle and are not to be used interchangeably. Patients receiving Calaspargase will only receive one dose in this cycle

± crisantapase (Erwinase®) or asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) may be substituted for allergy to Pegaspargase or Calaspargase. If reaction to Day 2 calaspargase requires Erwinia replacement, 2 courses of Erwinia (beginning at or around Day 2 and at or around Day 15) should be administered (i.e. 12 total Erwinia doses).

Block 2

Days	1	3	4	5	8	9	10	11	15	18	19	21
Ixazomib*	●		●		●				●	●		
Dexamethasone IV/PO (6mg/m^2)	→	→	→	→								

Vincristine IV (1.5mg/m^2)		●										
Methotrexate IV (1000mg/m^2)					●							
Pegaspargase IV / IM (2500 IU/m^2) √ ±						●						
OR Calaspargase IV (2500 IU/m^2) √ ±						●						
Cyclophosphamide IV (440mg/m^2)									→	→		
Etoposide IV (100mg/m^2)									→	→		
CNS 1/2: IT Methotrexate					●							
CNS 3: IT Triple					●							
Leucovorin IV/PO (15 mg/m^2)^							●	→				

√ Either Pegaspargase OR Calaspargase will be administered according to current approved labeling based on age and regional availability. Patients who start on either Pegaspargase or Calaspargase must continue the same treatment throughout the treatment cycle and are not to be used interchangeably.

± crisantapase (Erwinase®) or asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) may be substituted for allergy to Pegaspargase or Calaspargase. Six doses of replacement Erwinia should be given to replace either pegaspargase or calaspargase during Block 2

Optional Standard Maintenance

Days	1	2	5	8	11	15	18	22	28
Ixazomib*	●			●		●			
Vincristine IV (1.5mg/m^2)	●								
Prednisone (20mg/m^2/dose BID)	→	→							
Mercaptopurine (75mg/m^2/day)	→	→	→	→	→	→	→	→	→
Methotrexate 20mg/m^2/week	●			●		●		●	●
IT Methotrexate#	●								
Leucovorin IV/PO (5 mg/m^2 at hr 24 and 30 post-IT)^		●							

Optional per treating physician; or Triple IT: optional for CNS 3 patients only
*Ixazomib is a capsule that will be given orally. If you can't swallow a capsule, you will be given a liquid solution. Ixazomib will be given at different doses. The table below shows the doses of ixazomib planned in this study. Your doctor will discuss with you which dose of ixazomib will be administered.
^For patients with DS only (based on dates when IT MTX or ITT given)

Level	**Patients ≥ 1 year of age Dose**	**Patients < 1 year of age Dose**
-1	1.2 mg/m^2/day	0.04 mg/kg/day
1	1.6 mg/m^2/day	0.05 mg/kg/day
2	2 mg/m^2/day	0.07 mg/kg/day

Each treatment will last 4 weeks. At the end of each treatment course, you will have an evaluation to see how your leukemia is responding to therapy. Additional therapy is recommended after completion of this treatment and your doctor will discuss those options with you.

Medical Tests During Treatment

Whether you are on this study or not the following medical tests will be done to monitor for response to treatment as well as side effects related to treatment. You will have regular medical appointments throughout treatment. The timing of the appointments will be the same regardless if you participate in the research study. These include:

- Physical exams with vital signs
- Neurological Exams
- Blood tests to check your organ function including
  - CBC to look at your blood cells
  - Chemistries to look at elements and minerals in your blood
  - Blood tests to look at your liver and kidney function
- Bone Marrow Tests (including test for minimal residual disease)
- Lumbar Punctures
- Radiology scans such as a CT, MRI, or X-ray, if indicated

Tests for Research Purposes:

In addition to the routine tests listed above, we would like to do other tests while you are enrolled on the study.

We would also like to do some extra tests called biologic studies. These tests will help us learn more about Ixazomib on leukemia cells and may help children who receive this drug in the future. The information learned would not change the way you are treated, and the results of these tests will not be returned to you. Some of these tests are required and others are optional. Although these tests are very important part of how we will better learn to use this drug, it is your decision as to whether or not you agree to participate.

Biology Studies using Bone Marrow and Blood Samples (Optional)

When bone marrow testing is being done as part of your standard evaluation(s) before you begin therapy and during the first 24 hours of receiving Investigational Product (blood sample only), we would like to request extra samples (approximately ½ teaspoon bone marrow and 4 teaspoon of blood) at different time points to evaluate the effect of Ixazomib on your cells in the bone marrow and if sample permits to grow your cancer in a mouse to further study the effect of Ixazomib and intensive reinduction chemotherapy on proteins in those cells. Cells leftover from the research studies above will be stored for future proteomics research and TACL biology studies.

Upon the completion of this study, any leftover bone marrow and blood samples (including cells) and data from testing done on your samples will be stored within the TACL Central Biological Repository under the TACL T2016-005 study for use in future research studies.

Your leftover research samples (including cells) and data from testing done on your research samples being stored at Baylor College of Medicine and in the TACL Central Biorepository will be “coded.” “Coded” means that your leftover research samples and data will be assigned a unique code. Your leftover samples and data will not include your name or any other identifying information about you. The code that could be linked back to your identifying information will be kept separate from your research samples and data.

Your leftover research samples (including cells) and data being stored at Baylor College of Medicine and in the TACL Central Repository may be used by the researcher conducting this study or other researchers (at CHLA or elsewhere) for future research projects that are unrelated to the purpose of this study. This future research may be done without consulting you or obtaining consent (permission) for this additional use. Future TACL biology studies on samples stored in the TACL Central Repository might include whole genome sequencing.

Your coded leftover research samples (including cells) stored at Baylor College of Medicine and in the TACL Central Biorepository may also be used for commercial research. There are no plans for you to share in any profits generated for any discoveries made as a result of this research.

Information about Genetic Testing

Inside each cell in the human body, there are long and complex molecules called DNA. DNA stores the information that directs all cells in the body how to work. DNA is made up of many genes. Genes direct specific things like hair color or height.

When scientists look at the whole length of all your DNA molecules, this is called “whole genome” or “whole exome” testing. “Whole genome” or “whole exome” tests result in a unique set of genetic blueprints that can be used to identify you (like a fingerprint) and possibly your near blood relations.

If whole genomic sequencing is done on your leftover research samples stored in the TACL Central Biological Repository, the risks related to genetic analyses can be to individuals or groups. These harms include stigmatization and insurability. There is also a possibility that the results of the genetic testing could reveal both your risk of certain genetic disorders, and also suggest the risk of disease of close family. To reduce these risks, your samples will be stored and labeled with a code number as designed above. If the results are used in future research, the researchers will not be able to identify you. Information will not be recorded in your medical record.

There is a Federal law, called the Genetic Information Nondiscrimination Act (GINA), which generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law may protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

This Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

There may be other risks that are not known at this time. Tell the study investigator or study staff right away if you have any problems.

We will ask you about your decision about this optional procedure(s) at the end of this form. If you choose not to participate in the optional procedure(s), the data and specimens collected in this study will not be stored and used in future research studies.

PK Samples (Mandatory)
Doctors have developed test to study the levels of Ixazomib in the body. During therapy, researchers would like to draw additional blood at various time points. Any leftover blood that is not used for this test will be destroyed. Blood samples will be collected from all subjects during the study, the amount of the blood draw will be based upon your weight. Your doctor will discuss with you how much blood is required.

Phase 1:
Patients that are <20 kg will have 5 additional blood draws (approx.10mL, a little over 2 teaspoons), while patients ≥20 kg will have 16 additional blood draws during Block 1 (approx.32mL, a little over 2 tablespoons).

Phase 2:
Patients that are <20 kg will have 4 additional blood draws (approx. 8mL, about a teaspoon and half) while patients ≥20 kg will have 10 additional blood draws between Block 1 & Block 2 of treatment (approx.20mL, a little over 1 tablespoon).

Palatability Test

During the first block of treatment, a questionnaire will be completed after each dose of Ixazomib to gauge the smell and taste, using a 5-point facial scale.

Final Study Visit
Within 30 days after you finish the last dose of study drugs, your doctor will need to check to see how you are doing. The doctor will ask you how you feel, if you have trouble doing your daily routine, and what drugs you are taking. You will also have the following tests done:

- Physical exam, weight and vital signs
- CBC and chemistry blood tests

Follow-up Tests
After completing the treatment on this study we would like to continue to collect some medical information about how you are doing for as long as you are willing to let us or until the study is completely closed. We will collect information on how your ALL or LLy is doing, what kind of therapy you may be getting and if you have any long term side effects.

What are my responsibilities?

- During the study you will be asked to take all your chemotherapy drugs as prescribed. It is very important that you follow your doctor's instructions regarding when and how to take your study medications. Be sure to ask your study doctor or nurse if you have any questions about taking your study medications.

- If you experience any unusual side effects as explained by your study doctor, you should contact the study center immediately. You should also contact your study doctor if you are hospitalized for any reason during the study or within 30 days after completion of therapy.

How long will I be in the study?

You will be in the study to receive at least one course of therapy. After completing the study therapy, your doctor will discuss with you the options for additional treatment. These options will vary depending on whether or not your leukemia responded to the therapy. You will remain in study for approximately 24 months.

After completing the treatment on this study we would like to continue to collect some medical information about how you are doing for as long as you are willing to let us. We will collect information on how your ALL or Lymphoma is doing, what kind of therapy you may be getting and if you have any long term side effects.

Can I stop being in the study?

Yes. You can decide to stop at any time. Your clinical care will not be affected by your decision to withdraw. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. You will be asked to visit the hospital or clinic for some follow-up tests to make sure all the side effects you may have experienced have gone away.

It is important to tell your doctor if you are thinking about stopping so any risks of the study treatment and chemotherapy drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your doctor may stop you from taking part in this study at any time without your permission if he/she believes it is in your best interest; if you do not follow the study rules; if you become pregnant or begin to breast feed; or if the study is stopped.

What side effects or risks can I expect from being in the study?

All people who receive cancer treatment are at risk of having side effects. In addition to killing leukemia cells, chemotherapy drugs can damage normal tissues and produce side effects. Side effects are usually reversible when the medication is stopped, but occasionally can persist and cause serious complications or death. The therapy used in this clinical trial is intensified so that it can kill cancer cells quickly before they can become resistant to treatment. Protocols used to treat relapsed leukemia are more intense than are those to treat newly diagnosed disease. It is not possible to predict whether the side effects listed below, or other rare side effects may occur. Side effects can be increased when chemotherapy drugs are combined.

Common side effects include nausea, vomiting, hair loss and fatigue. Chemotherapy causes temporary bone marrow depression. Bone marrow depression results in a decreased production of red cells causing anemia; decreased platelet production causing bruising and an increased chance of bleeding; and decreased white cell production, causing a risk of serious and potentially life threatening infections. Red blood cell and platelet transfusions may be required.

Risks of having the bone marrow procedure include bleeding, chance of an infection and long lasting pain at the place where the needle is inserted into the bone.

Each drug will have a unique set of side effects. Side effects related to drugs occur in people at different rates or frequencies.

STUDY DRUG

There are risks to taking part in any research study. During the study, you may have problems or discomforts and risks from Ixazomib, Ixazomib and other drug combinations, and/or study procedures. The more commonly occurring discomforts and risks are listed below, as are the rare but serious discomforts and risks. You should discuss these with your study doctor. There is always the possibility that unknown risks may occur, however your doctor will watch closely for problems or discomforts and risks. Many discomforts and risks go away shortly after treatment is stopped or with treatment for the discomforts and risks, but in some cases discomforts and risks may be serious, long- lasting or permanent and may even result in hospitalization or death.

If any discomforts and risks occur, you must tell your study doctor or study staff, even if you do not think they are related to the study drug.

POTENTIAL DISCOMFORTS AND RISKS OF IXAZOMIB

Based on studies of Ixazomib it is possible to predict some of the discomforts and risks. However, it is possible that Ixazomib may cause risks that have not yet been observed in patients. The following risks might be seen:

- Low platelet count which may increase the chance of bleeding
- Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body Nausea

- Vomiting
- Diarrhea
- Numbness or tingling or pain feelings in hands and feet
- Swelling or fluid buildup in the arms or legs
- Flu-like symptoms and other upper respiratory tract infections
- Arthralgia or joint pain
- Lung infections including pneumonia, bronchitis, or pneumonitis
- Herpes Zoster that can sometimes cause local pain that may last after recovery from the skin rash and does not go away from some time

Other discomforts and risks reported in studies with Ixazomib, which may have been due to the patient's disease, Ixazomib, other medications, or some combination of these include:

- Not feeling like eating
- Electrolyte imbalance (blood chemical imbalance)
- Loss of water from the body (dehydration; because of vomiting and/or loose stools
- High blood creatinine and renal failure which means your kidneys are having trouble working well; Patients who had lost body water (dehydration) because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis)
- Feeling short of breath or difficulty breathing
- Feeling tired or weak
- Chills
- Cough
- Fever
- Headache
- Pain in the abdomen or back
- Muscle weakness
- Feeling dizzy or dizziness
- Lowered blood pressure that can commonly cause you to feel light headed, faint or pass out when you stand up
- Lowered white blood cells called lymphocytes
- Lowered red cells or anemia which may make you feel tired
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever
- Constipation
- Pain (muscular) in extremities
- Distortion of the sense of taste i.e. an abnormal or impaired sense of taste
- Trouble falling asleep, staying asleep or both

Some discomforts and risks occur with lesser frequency (<1%) than those mentioned above, should be noted because they are severe, life-threatening or fatal. With limited experience and because these events occurred while patients were receiving other drugs as well, we do not know if ixazomib causes such problems. Severe, life-threatening or deadly conditions that may involve rash, blistering, skin peeling and mouth sores including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute febrile neutrophilic dermatosis (Sweet's syndrome) and pemphigus vulgaris, have been reported in ixazomib studies when given in combination with other drugs. These rashes are disorders of the immune system, which differ from regular skin rashes and are generally more severe.

In addition, two rare neurological conditions have been reported in patients on ixazomib (frequency <1%). Posterior reversible encephalopathy syndrome (PRES) which affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible.. Transverse myelitis, also a rare condition (<1%), is an inflammatory disease causing injury to the spinal cord which has been reported in a patient receiving ixazomib. This condition may cause varying degrees of muscle weakness, reduced movement in legs, changes in the feelings of the toes and feet, unusual muscle tightness, feelings of pain, changes in bowel (constipation) or urinary (loss of control) function or loss of leg movement. In general, recovery may be partial, complete, or not at all but most patients experiencing transverse myelitis have good to fair recovery of symptoms. We do not know whether Ixazomib causes transverse myelitis, however, as it happened to a patient receiving ixazomib, we are not able to exclude the possibility that ixazomib may have contributed to transverse myelitis.

Progressive multifocal leukoencephalopathy (PML) is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. PML has been observed rarely (<0.1 %) in patients taking ixazomib. It is not known whether ixazomib may contribute to the development of PML.

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS), are rare, serious blood disorders that cause low levels of platelets and red blood cells, and result in blood clots in small vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders can occasionally be fatal. TMA, TTP, and HUS have been seen rarely (<0.1%) in patients treated with ixazomib.

Overdose has been reported in patients taking Ixazomib. Reports of accidental overdose have been associated with risks such as nausea, lung infections including aspiration pneumonia, multiple organ failure, and death. It is important to take only one dose of Ixazomib at a time, and only at the prescribe intervals.

Ixazomib should not be taken if you have ever had an allergic reaction to the active substance or any of the inactive ingredients using in its formulation.

The following side effects may also be a risk with ixazomib because they have been reported with another proteasome inhibitor, bortezomib (Velcade), in patients with diseases requiring this type of treatment, or in patients who receive ixazomib in combination with other drugs for cancer treatment:

- Rapid death of cancer cells that may let large amounts of the cells into the blood that injure organs, such as kidneys (this is referred to as tumor lysis syndrome);
- Worsening of your heart function (congestive heart failure) that may require additional drugs for treatment or hospitalization;
- Disorders of your lung that could be serious enough to result in death

Other drugs and supplements may affect the way ixazomib works. Tell your doctor about all drugs and supplements you are taking while you are in this study.

RISK TO THE UNBORN CHILD (MEN AND WOMEN)

Female Subjects: We do not know if the study drug Ixazomib will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnancy women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/infant, you should not become pregnant or nurse a baby while on this study.

You must have a negative pregnancy test prior to enrolling in the study

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation: you had the ovaries or the uterus removed; or you are post-menopausal), you must use two effective methods of birth control from the time of signing the information consent form, for the entire study drug treatment period (including interruptions in treatment), and for 6 months after completing study drug treatment. It is strongly recommended that at least one of these two methods be highly effective (see example below).

Highly effective methods	**Other effective methods (barrier)**
Intra-uterine devices (IUD)	Latex or non-latex condom with or without a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or	Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

You must us birth control methods as directed above, unless you completely avoid having heterosexual intercourse.

Male subjects: We do not know if using ixazomib will affect sperm, Therefore, due to potential risk, you should not get your partner pregnant during the study drug treatment period (including interruptions in treatment). Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex or non-latex condom with or without a spermicidal agent) during the entire study drug treatment period, and for 6 months after completing study drug treatment, Or, you should completely avoid having heterosexual intercourse.

Highly effective methods	**Other effective methods (barrier)**
Vasectomy	Latex or non-latex condom with or without a spermicidal agent
	Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

All subjects (male or female): If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately, and the pregnancy will be followed until conclusion.

If you do not understand what any of these discomforts and risks mean, please ask the study doctor or study staff to explain the terms to you.

Tables listed below are the additional chemotherapy drugs to be used and outlines potential risks and discomforts.

Asparaginase (Pegaspargase OR Calaspargase):

More Likely	Less Likely	Rare but Serious
• An increase in the level of ammonia that is found in the blood • A decrease in levels of factors in the blood that help your blood to clot normally • A feeling of extreme tiredness not relieved by sleep • Weakness • Diarrhea	• Rashes, hives, swelling of the lips • Feeling short of breath or shortness of breath • Some sort of allergic reaction such as a rash, hives or fever that may require pretreatment with antihistamines prior to the injection • Puffiness or swelling around the eyes • Fluid build-up in the tissues or Fluid retention • High levels of sugar in the blood that may require treatment • Elevation in the blood of certain enzymes or bilirubin found in the liver which may mean liver irritation or damage • High levels of uric acid in the blood which could damage the kidneys • Headache • Dizziness • Chest pain • A fast heartbeat which may cause pain in the chest • A decrease or an increase in blood pressure • Loss of desire to eat or appetite • Weight loss • Mild nausea and/or vomiting • Muscle and joint aches and pains • Numbness and tingling in the fingers and toes • Chills and fever • Changes in your mood such that you feel depressed, irritable, confused or have hallucinations (see or hear things that are not there) • An increase in the levels of lipids (fats) in your blood which if prolonged could lead to heart problems later in life • Shakiness or tremor which may cause jerky movements • Pain in the abdomen (belly) • Too much gas produced in the intestines	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever • Irritation of the small airways of your lungs that can make you cough and wheeze • Seizures • Coma • Sudden damage to the red blood cells (hemolytic anemia) which could cause a rapid decrease in the number of red blood cells such that you would be tired and weak and feel short of breath and may require a blood transfusion • Temporary decrease in blood to the brain which can lead to temporary loss of consciousness • A bleeding disorder that can lead to bleeding from many areas of the body or excessive clotting in blood vessels including those that lead to the brain • Damage to the bladder which can lead to large amounts of blood in the urine, pain and the urge to urinate frequently and also scarring of the bladder • High levels of nitrogen and/or a chemical (creatinine) in the blood which may indicate that the kidneys are not working as well as normal • Severe kidney damage • Severe damage to the liver which can lead to a fatty and enlarged liver, inflammation and/or scarring which could lead to a yellow appearing skin, and fluid collection in the abdomen (belly) which makes it look larger • Reduced ability of the body to fight infection which can lead to infections including severe blood infections which will need to be treated and may be life threatening, infections of the

More Likely	Less Likely	Rare but Serious
	• Inflammation of the pancreas (an organ in the abdomen which produces insulin and certain digestive chemicals) which may affect the function of the pancreas and which may cause pain in the abdomen (belly)which can be severe and may increase the blood sugar • Elevations of certain chemicals in the blood which may indicate damage to the pancreas • Fewer white blood cells, red blood cells and platelets in the blood ○ a low number of white blood cells can make it easier to get infections ○ a low number of red blood cells can make you feel tired and weak ○ a low number of platelets causes you to bruise and bleed more easily	valves in the heart, the bladder and other areas of the body

Erwinia Asparaginase:
If you develop an allergic reaction to asparaginase (Pegaspargase or Calaspargase), you may be treated with crisantapase (Erwinase®) if available. This preparation has been given to hundreds of children over many years and many of the side effects are similar to those that occur with the other forms of asparaginase.

Another alternative if you are not able to take Pegaspargase or Calaspargase is Erwinia chrysanthemi (recombinant)-rwyn (Rylaze ®) (given into the muscle). The side effects are the same as Erwinia asparaginase.

More Likely	Less Likely	Rare but Serious
	• Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing. • Allergic reaction which can be life-threatening and potentially fatal. This reaction requires immediate medical treatment. It may include fever, chills and skin rash. Less commonly wheezing, shortness of breath, swelling of the throat, drop	• Inflammation of the pancreas (an organ in the abdomen which makes insulin and certain digestive chemicals) which causes severe pain in the abdomen (belly) and back and may increase the blood sugar • Formation of blood clots that plug blood vessels and can lead to pain and swelling in the area of the clot. Such clots may break loose and travel to another area. They can cause damage or be life-threatening depending on where they go.

	in blood pressure, and rapid heart rate may occur. • Hives; red and sometimes itchy bumps on the skin. • Local allergic reactions including rashes and hives around the site of the injection	• Excessive or uncontrolled bleeding which can occur in the head, stools, the nose, urine and other parts of the body. • Sudden and temporary loss of blood flow and oxygen to the brain causing problems with vision, dizziness, weakness and numbness (especially in one side of the body), and trouble speaking. Also called mini stroke. • A bleeding disorder in which small blood clots develop throughout the bloodstream blocking small blood vessels and depleting platelets and clotting factors needed to control bleeding. This condition can lead to bleeding from many areas of the body and can be life-threatening. • Fever • Abnormal control of blood sugar level • Increase in the blood level of certain enzymes or bilirubin (a waste product that passes through the liver) which could indicate liver irritation or damage • High blood sugar which may require treatment with insulin • An increase in the level of ammonia that is found in the blood • Vomiting • Nausea • Belly pain • Headache • Diarrhea • Weight loss • Seizures; sudden, uncontrolled muscle spasm and loss of consciousness resulting from abnormal brain function.

Cyclophosphamide:

More Likely	Less Likely	Rare but Serious
• Loss of appetite • Nausea • Vomiting • Fewer white blood cells in the blood • Hair loss • Decreased ability of the body to fight infection	• Abnormal hormone function which may lower the level of salt in the blood • Abdominal pain • Diarrhea • Fewer red blood cells and platelets in the blood	• Heart muscle damage which may occur with very high doses and which may be fatal • Abnormal heart rhythms • Damage and scarring of lung tissue which may make you short of breath

More Likely	Less Likely	Rare but Serious
• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children	• Bleeding and inflammation of the urinary bladder • Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children • Temporary blurred vision • Nasal stuffiness with IV infusions • Skin rash • Darkening of areas of the skin and finger nails • Slow healing of wounds • Infections	• A new cancer or leukemia resulting from this treatment. • Damage or scarring of urinary bladder tissue • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever • Infertility which is the inability to have children

Doxorubicin:

More Likely	Less Likely	Rare but serious

▪ Nausea
▪ Vomiting
▪ Temporary hair loss
▪ Loss of appetite
▪ Pink or red color to urine, sweat, tears, saliva
▪ Fewer white blood cells, red blood cells and platelets in the blood.
  • A low number of red blood cells can make you feel tired and weak
  • A low number of white blood cells can make it easier to get infections
  • A low number of platelets causes you to bruise and bleed more easily
▪ Abnormal heart rhythm that is unlikely to have any noticeable effects on your heart function
▪ Decreased ability of the body to fight infection
	▪ Inflammation and/or sores in the mouth, throat and/or esophagus
	▪ Diarrhea
	▪ Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid
	▪ Dark discoloration of the hands, feet and under the fingernails
	▪ Rash
	▪ Thickening and hardening of the veins through which the medication is given
	▪ Damage to the liver
	▪ Tearing and inflammation of the eyes
	▪ Redness and burning at sites which have received radiation in the past
		▪ Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		▪ Ulceration of the lower intestinal tract
		▪ An irregular heart beat which can be life-threatening
		▪ Severe damage to the heart muscle which may lead to severe heart failure
		▪ A new cancer or leukemia resulting from this treatment.
		▪ Damage to the skin if the medication leaks from a vein

Etoposide:

More Likely	Less Likely	Rare but Serious
• Nausea and vomiting • Hair Loss	• Loss of appetite	• Damage to the liver • Severe allergic reaction which can be life threatening with shortness

• A feeling of weakness or tiredness • Fewer red and white blood cells and platelets in the blood • A low number of red blood cells can make you feel tired and weak • A low number of white blood cells can make it easier to get infections • A low number of platelets causes you to bruise and bleed more easily	• Decreased blood pressure during the infusion which may require treatment • rashes • Diarrhea • Pain in the abdomen • Mouth sores • Tingling sensation or loss of sensation in fingers or toes • A feeling of extreme tiredness or weakness • The finger or toe nails may loosen from their nail beds • Inflammation of the vein through which the medication was given • Chest pain	of breath, low blood pressure, rapid heart rate chills and fever • A new cancer or leukemia resulting from this treatment • Severe rashes which can result in loss of skin and damage to mucous membranes • Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children • Damage to the heart muscle which may make you feel tired, weak, feel short of breath, and retain fluid

Intrathecal Triple (Methotrexate/Hydrocortisone/Cytarabine):

More Likely	Less Likely	Rare but Serious
• None	• Headache • Abnormally high number of cells in the spinal fluid • Learning disability • Nausea and Vomiting • Fever • Rash • Seizures • Drowsiness • Stiff neck • Irritation of tissues in the brain/spinal cord • Unsteady walk	• Partial paralysis • Damage to brain tissue • Increasingly poor nervous system function • Fewer red and white blood cells and platelets in the blood

Leucovorin Calcium:

More Likely	Less Likely	Rare but Serious
• None	• Hives	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever • Seizure

Intrathecal Methotrexate:

More Likely	Less Likely	Rare but Serious
▪ None	▪ Headache ▪ Abnormally high number of cells in the spinal fluid ▪ Learning disability ▪ Vomiting ▪ Fever	▪ Seizures ▪ Partial paralysis ▪ Damage to brain tissue ▪ Increasingly poor nervous system function

More Likely	Less Likely	Rare but Serious
	▪ Rash ▪ Drowsiness ▪ Stiff neck ▪ Irritation of tissues in the brain/spinal cord ▪ Unsteady walk	▪ Fewer red and white blood cells and platelets in the blood • a low number of red blood cells can make you feel tired and weak • a low number of white blood cells can make it easier to get infections • a low number of platelets causes you to bruise and bleed more easily

Vincristine Sulfate:

More Likely	Less Likely	Rare but Serious
▪ Constipation ▪ Hair loss ▪ Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes ▪ Loss of deep tendon reflexes (such as the "knee jerk") noted only on physical exam	▪ Jaw pain ▪ Headache ▪ Muscle Weakness ▪ Pain and bloating in your abdomen ▪ Numbness and tingling ▪ Wrist or foot drop ▪ Abnormal walk with foot slapping ▪ A drop in white blood cells, red blood cells and platelets in the blood ▪ A low number of red blood cells can make you feel tired and weak. ▪ A low number of white blood cells can make it easier to get infections. ▪ A low number of platelets can make you bruise and bleed more easily.	▪ Complete stoppage of your intestinal activity which can result in intestinal blockage ▪ If the drug leaks out of the vein when being administered it can cause damage to nearby tissue ▪ Seizures ▪ Vocal cord paralysis ▪ Difficulty breathing ▪ Inability to walk ▪ Decreased ability to hear clearly ▪ Dizziness ▪ Difficulty with urination or increase desire to urinate ▪ Drooping eyelids ▪ Double vision, difficulty seeing at night

Dexamethasone:

Likely	Less Likely	Rare
• Overeating • Difficulty sleeping or falling asleep • Decreased ability of the body to fight infection • Personality changes with mood swings • Changes in hormone production that cause weight gain especially around the abdomen and shoulders, puffy cheeks, muscle	• Upset and irritated stomach with heartburn • High blood sugar which may require treatment • Red face • Poor wound healing • Infections • Fluid retention • Stretch marks and easy bruising of the skin • Muscle weakness	• Abnormal amounts of uric acid in the blood • Inflammation of the pancreas • Increased pressure in the eyes High blood pressure • Serious changes in mood, personality and/or severe depression • Dizziness • Headache

Likely	Less Likely	Rare
weakness and make your body less able to deal with stress • Pimples	• Lessening of calcium in the bones making them more susceptible to fracture • Cataracts which are usually more reversible in children	• Bone Fractures • Slowed growth • Stomach ulcers • Stomach and intestinal tract bleeding from ulcers • Increased pressure in the brain which can lead to difficulty seeing, pressure in the eyes and headache • Damage to the joints which can result in pain and loss of motion usually involving the joints of the hip and knee

Reproductive risks

Because the drugs in this study may affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not breast-feed a baby while on this study. It is a condition of this study that adequate birth control methods be used by all participants while enrolled in the study. Examples of these include total abstinence (no sex), oral contraceptives ("the pill"), an intrauterine device (IUD), Levonorgestrol implants (Norplant), or medroxyprogesterone acetate injections (Depo-provera shots). If one of these methods of birth control cannot be used, contraceptive foam with a condom is recommended. Contraception methods is required during the entire study treatment including breaks in treatment, and a minimum of 6 months after the last dose of study drug. Ask your doctor about counseling and more information about preventing pregnancy.

Female patients who become pregnant or male patients whose partner becomes pregnant will be given instructions for discontinuation of study medication and will be removed from study. The study doctor will discuss the requirements for pregnancy outcome follow-up.

Confidential Information

There is the potential risk of accidental disclosure (release) of confidential information when you participate in research. Please see the "Will my medical information be kept private?" section of this document for more details.

Developing a Second Cancer

It is possible that you may develop a second form of cancer as a result of this treatment. Experience so far suggests that the chance of this happening is very small. Not enough information has been gathered in children to be able to give an accurate prediction, although it may be in the range of one in every 50 to 800 children treated.

Are there benefits to subjects taking part in the study?

Participation in this study may or may not benefit you. Participating in this study will not cure your relapsed leukemia or lymphoma. Based on experience with the drugs used in the treatment plan, researchers believe this therapy

may cause your leukemia to stop growing or go into remission for a period of time. Your cancer may not have any response to the therapy received while participating in this study.

It is hoped that the information learned from this study may help future children or young adults with relapsed ALL and LLy.

Your participation in this research study may contribute to the development of commercial products from which Takeda or others, may derive an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

What other choices do I have if I do not take part in this study?

You do not have to participate in this study to receive treatment for recurrent leukemia. There is no "standard" therapy for recurrent leukemia. Most treatment plans have used drugs similar to those used in this protocol, although these drugs may be given in different combinations, and at different times. You can receive other combinations of chemotherapy without participating in this study.

As an alternative to this study, you may decide you don't want additional treatment for your relapsed leukemia. You will always receive medicines to help you feel more comfortable and deal with problems caused by your cancer or treatment whether you participate in this study or not.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law.

Members of the research team and, if appropriate, your primary care physicians and nurses will know that you are a research subject. All results will be kept confidential, but may be made available to you, and/or your physician if you wish. Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately. You may read your medical record. The records are available to those caring for you at this hospital.

Organizations that may inspect/or copy your research records for quality assurance and data analysis may include but not limited to:

- Therapeutic Advances in Childhood Leukemia Consortium (TACL)
- The United States Food and Drug Administration (FDA)
- Therapeutic Goods Administration, Australia
- The Department of Health and Human Services (DHHS)
- The Institutional Review Board (IRB) of CHLA - Committee on Clinical Investigations

As a result, these organizations may see your name; but they are bound by rules of confidentiality not to reveal your identity to others. These organizations, and Takeda, its collaborators or designees, will also have access to information about you and the study data in a form that does not mention your name but will instead be identified by a code number and your initials. Your study doctor is responsible for keeping a list of codes to make it possible to link your code to your name. This list will be kept in a safe place to make sure that in an emergency you can be identified and contacted. Reasonable steps will be taken to protect your right to privacy. No information about you,

or provided by you during the research, will be shared with others without your written permission, except as explained below:

- If necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- If required by law (i.e., child abuse, reports of certain infectious diseases)

The information collected will be used to meet the purpose of this clinical study. In addition, this information may be added to research databases and used in the future to

- Study other therapies for patients,
- Develop a better understanding of diseases included in the study, and
- Improve the efficiency, design and methods of future studies.

The coded information may be used by or sent to parties for clinical research, safety-reporting, other study-related uses described in this form and/or support applications to market the studied drug in the United States and in other countries. Some of these countries may not have data protection or privacy laws that offer the same level of protection as the data protection and privacy laws in your country. The study information may also be used in reports of the study or for scientific publications and presentations that will not identify study participants by name.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What are the costs of taking part in this study?

The health care costs during your participation in this study that are considered part of the standard treatment of your disease will be billed to your insurance or other third-party payer. This includes blood tests, hospitalizations, procedures that will be done and medications.

You will not have to pay for the following tests that will be done for research purposes only.

- Test for how the Ixazomib are affecting your leukemia cells
- The study drug Ixazomib will be supplied by Takeda Pharmaceuticals Company Limited

Your family is responsible for other costs which may result from your participation in the study, such as, but not limited to, time off of work, car fare, baby sitter fees, and food purchased while at the hospital, etc. You will not receive any type of payment for participating in this study. Taking part in this study may lead to added costs to your insurance company. Please ask about any expected added costs or insurance problems.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at *http://cancer.gov/clinicaltrials/understanding/insurance-coverage* . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you

have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study, the institutions taking part in the study, and Takeda will not pay for such medical treatment and are not responsible for any underlying illnesses or the worsening of your disease.

What are my rights if I take part in this study?

Taking part in this study is voluntary. You may choose not to participate in this study. If you decide not to participate, you will not be penalized and you will still receive the standard treatment.

If you choose to participate, you may discontinue your participation in the study at any time. If you discontinue participation in the study, physicians and hospital personnel will still take care of you.

You also have the right to know about new information that may affect your health, welfare, or your willingness to participate in the study. You will be provided with this information as soon as it becomes available.

Whether you participate or not, you will continue to get the best medical care this hospital can provide.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[*name of center*] Institutional Review Board (a group of people who review the research to protect your rights) at* _____ *[*telephone number*]. [*Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.*]*

Where can I get more information?

Call the National Cancer Institute's Cancer Information Service:
1-800-4-CANCER (1-800-422-6237) OR 1-800-332-8615 (for the hearing impaired)

- You will be given a copy of this consent form.
- You will be given a copy of this treatment plan upon request.
- CancerNet™: http:/cancernet.nci.nih.gov This site provides accurate cancer information including the Physicians Data Query (PDQ). The PDQ is the National Cancer Institute's comprehensive cancer database. It contains peer-reviewed summaries on cancer treatment, screening, prevention, and supportive care; a registry of about 1,700 open and 10,300 closed cancer clinical trials from around the world; and directories of physicians, genetic counselors, and organizations that provide cancer care.
- Visit the TACL Consortium Website at https://tacl.chla.usc.edu

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. In case patients or their legal guardians have questions about reporting product complaints you may contact the treating physician office to obtain more details.

CONSENT FOR OPTIONAL STUDIES FOR RESEARCH

THESE TESTS ARE OPTIONAL. YOU MAY STILL PARTICIPATE IN THE STUDY EVEN IF YOU DO NOT AGREE TO THESE TESTS.

Biology Studies using Bone Marrow Samples
When bone marrow testing is being done as part of your standard evaluation(s) before you begin therapy and during the first 24 hours of receiving ixazomib, we would like to request extra samples (approximately ½ teaspoon bone marrow and 4 teaspoon of blood) at different time points to study the effect of Ixazomib on your cancer cells in the bone marrow and blood.

The tests may help us to better learn how this drug may work. Please indicate by initialing below whether you choose to participate in the biology studies.

If you consent to this additional testing, your information resulting from the testing will be used as described above.

Mark your choice and sign your name and the date

YES, I agree to have bone marrow drawn on day 1 of block 1 for tests on cancer cells.

_____ initials of subject (if subject is 14 years or older)

_____ initials of parent/legal guardian (if subject is a minor)

_____ initials of parent/legal guardian (if subject is a minor)

NO, I do not agree to have bone marrow drawn on day 1 of block 1 tests on cancer cells.

_____ initials of subject (if subject is 14 years or older)

_____ initials of parent/legal guardian (if subject is a minor)

_____ initials of parent/legal guardian (if subject is a minor)

SIGNATURE OF RESEARCH SUBJECT

Your signature below indicates:

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You agree to participate in this research study; and
- You will be given a copy of the signed permission form.

_____
Name of Subject

_____ _____
Signature of Subject Date

SIGNATURE OF PARENT(S)/GUARDIAN (if the subject is a minor)

Your signature below indicates that you have read this document; understand its meaning; have had a chance to ask questions; have had these questions answered to your satisfaction; and agree to your child's participation in this research study. You have been given a signed copy of this assent/permission form.

_____	_____
Name(s) of Parent(s)/Guardian	Name(s) of Parent(s)/Guardian
_____	_____
Signature of Parent (Guardian)	Date
_____	_____
Signature of Parent (Guardian)	Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject and/or the subject's parent(s)/guardian(s) and have answered all of their questions. I believe that they understand the information described in this document and freely give consent/permission/assent to participate.

_____
Name of Investigator/Person obtaining consent

_____	_____
Signature of Investigator/Person obtaining consent	Date

SIGNATURE OF WITNESS (if applicable)

My signature as witness certified that the subject and/or the subject's parent(s)/guardian(s) signed this permission form in my presence as their voluntary act and deed.

_____
Name of Witness

_____	_____
Signature of Witness	Date

APPENDIX I : PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
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.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
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	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: CYP3A4 STRONG INDUCERS

The use of STRONG CYP3A4 INDUCERS should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy if reasonable alternatives exist. This is NOT an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

• Barbiturates	• Phenobarbital
• Carbamazepine	• Phenytoin
• enzalutamide	• Primidone
• fosphenytoin	• Rifampin
• St. John's wort	•

APPENDIX III: PHARMACOKINETIC WORKSHEET – T2017-002 IXAZOMIB STUDY PHASE 1

TACL Registration #: _____ BSA (m2): _____

Height (cm): _____ Assigned Dose (mg/m^2): _____

Weight (kg): _____ Actual dose (mg): _____

CRC Name: _____ CRC Email Address: _____

Block 1 Day1: Date:_____ Time of Administration:_____

Patient **<20 kg** PK Schedule

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
1	4		72 Hours(to be collected before dose #2 on Day 4 of Block 1)			

Block 1 Day 11: Date:_____ Time of Administration:_____

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
2	11		Pre-dose (- 2 hours)			
3	11		30 Min (+/- 5 mins)			
4	11		4 Hours (+/- 30 mins)			
5	14		72 Hours (+/- 3 hours)			

Patient **≥20 kg** PK Schedule Below:

Block 1 Day 1: Date:_____ Time of Administration:_____

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
1	1		30 Min (+/- 5 mins)			
2	1		1 Hour (+/- 15 mins)			
3	1		2 Hours (+/- 15 mins)			
4	1		4 Hours (+/- 30 mins)			
5	1		8 Hours (+/- 1 hour)			
6	2		24 Hours (+/- 1 hour)			
7	4		72 Hours(to be collected before dose #2 on Day 4 of Block 1)			

Block 1 Day 11: Date:_____ Time of Administration:_____

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
8	11		Pre-dose (- 2 hours)			
9	11		30 Min (+/- 5 mins)			
10	11		1 Hour (+/- 15 mins)			
11	11		2 Hours (+/- 15 mins)			
12	11		4 Hours (+/- 30 mins)			
13	11		8 Hours (+/- 1 hour)			
14	12		24 Hours (+/- 1 hour)			

15	14		72 Hours (+/- 3 hours)			
16	22		264 Hours (+/- 8 hours)			

PHARMACOKINETIC WORKSHEET – T2017-002 Ixazomib Study Phase 2

TACL Registration #: _____ BSA (m2): _____

Height (cm): _____ Assigned Dose (mg/m^2): _____

Weight (kg): _____ Actual dose (mg): _____

CRC Name: _____ CRC Email Address: _____

Block 1 Day 1: Date:_____ Time of Administration:_____

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
1	4		72 Hours (to be collected before dose #2 on Day 4 of Block 1)			

Block 1 Day 8: Date:_____ Time of Administration:_____

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
2	8		Pre-dose (- 2 hours)			

Block 1 Day 11: Date:_____ Time of Administration:_____

Patient **<20 kg** PK Schedule

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
3	11		Pre-dose (- 2 hours)			
4	14		72 Hours (+/- 3 hours)			

Patient **≥20 kg** PK Schedule

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
3	11		Pre-dose (- 2 hours)			
4	11		30 Min (+/- 5 mins)			
5	11		2 Hours (+/- 15 mins)			
6	11		4 Hours (+/- 30 mins)			
7	14		72 Hours (+/- 3 hours)			

Block 2 PK only for Patients ≥20 kg below:

Block 2 Day 1: Date:_____ Time of Administration:_____

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments

1	1		Pre-dose (- 2 hours)			

Block 2 Day 15: Date:_____ Time of Administration:_____

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
2	15		Pre-dose (- 2 hours)			

Block 2 Day 18: Date:_____ Time of Administration:_____

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments
3	18		Pre-dose (- 2 hours)			

Blood Collection procedure:
2 ml PK samples should be collected into tubes provided in the ixazomib PK collection kit. This will be provided by Covance.

Materials
Blood samples for PK assessment must be collected in 2-mL vacutainer tubes containing K_2EDTA as the anticoagulant. Resulting blood and plasma PK samples must be stored in plastic storage tubes with caps. No blood collection tubes with separation gel should be used.

Plasma (0.5 mL) is stored in tubes containing 250 mg lyophilized citric acid.

Preparation of Plasma Pharmacokinetic Samples

1. Draw blood into labeled and chilled 2-mL lavender top K_2EDTA vacutainer tube.

2. Mix the blood with the anticoagulant by gently inverting the tube 8-10 times and immediately place on wet ice.

3. Centrifuge the blood samples for 10 minutes at 1000 x g at 4º C in a refrigerated centrifuge within 10 minutes of sample collection.

4. Immediately following centrifugation, gently remove the plasma from the packed cells and aliquot into transfer vials filled with lyophilized citric acid. **Each aliquot should contain exactly 0.5 mL of plasma**.

5. Vortex split tubes thoroughly. Any remaining plasma post-split 1/split 2 sample aliquots should be discarded following appropriate biohazard disposal procedures.

NOTE: If < 0.5 mL plasma is obtained post centrifugation, do not process or store split 1 or split 2, record split 1: ISV (Insufficient Sample Volume), split 2: ISV**. If < 1.0 mL plasma is obtained post centrifugation, process and store split 1 according to procedure; do not process or store split 2, record split 2: ISV.** Discard remaining plasma using appropriate biohazard waste disposal procedures.

6. Replace cap on tube and freeze the samples immediately at -70°C.

Note: No more than 60 minutes should elapse between blood collection and freezing the plasma samples.

7. Keep samples frozen at -70°C or lower until shipment.

Note: Wet ice is defined as a mixture of ice and water.

Specimen Labeling:
Each tube must be labeled with the study ID number, along with the date and time of the sample was obtained. No personal identifying patient information should be included in the specimen or transmittal form.

Specimen Packaging and Shipping:
Covance Clinical Laboratory Services
8211 Scicor Drive, Indianapolis, IN 46214 USA

APPENDIX IV: GUIDANCE FOR DETERMINING PREVIOUS CUMULATIVE ANTHRACYCLINE DOSE

Total Anthracycline Calculation Worksheet

Instructions:
In order to calculate the total anthracycline received by a patient, you will need to review the patient's previous treatment. You will need to document **each dose** of anthracycline chemotherapy prescribed and received by the patient.
Step 1: Indicate which drug the patient received.
Step 2: Enter the prescribed dose for that drug per the chemotherapy roadmap/orders. Be sure to list all doses.
Step 3: Enter the corresponding conversion factor for the drug given.
Step 4: Multiply the prescribed dose by the conversion factor and enter the result in the "Total Anthracycline" column.
Step 5: After you have completed this worksheet for all doses, add all the total doses to obtain the Total Cumulative Dose.

Drug	Prescribed Dose The prescribed dose is the dose of chemotherapy written in the protocol. It will be listed as mg/m^2. (It is not the actual dose received by the patient)	Conversion Factor Doxorubicin = 1 Daunorubicin = 0.5 Epirubicin: = 0.67 Idarubicin = 5 Mitoxantrone = 4	Total Anthracycline
☐ Doxorubicin ☐ Daunorubicin ☒ Idarubicin ☐ Mitoxantrone ☐ Epirubicin	**EXAMPLE:** **10 mg/m^2**	**5**	**50 mg/m^2**
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone ☐ Epirubicin			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone ☐ Epirubicin			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone ☐ Epirubicin			
		Total Cumulative Dose	

Calculate cumulative anthracycline dose (all based on doxorubicin):
Daunorubicin: x 0.5
Doxorubicin: x 1
Epirubicin: x 0.67
Idarubicin: x 5
Mitoxantrone: x 4

Reference: http://survivorshipguidelines.org/

APPENDIX V: EVALUATING MECHANISMS OF IXAZOMIB RESPONSE AND RESISTANCE IN LEUKEMIA; IDENTIFYING BIOMARKERS AND MECHANISMS OF CHEMOTHERAPY RESISTANCE

Eligible samples:

All pre-treatment bone marrow samples are eligible. Peripheral blood samples should be sent to the Horton lab only if the patient samples meet the following criteria:

Eligible patients must have an initial absolute blast count of **at least 1000 blasts/µL**. To calculate the absolute blast percentage, multiply the total WBC by the % peripheral blasts:

(WBC)(% blast)(1000) = absolute blast count/µL

As an example, if the patient has a WBC of 10 and 50% blasts, the absolute blast count is:

(10)(.5)(1000) = 5000/µL

If the initial % blasts is unknown, send peripheral blood samples only if the total WBC is more than 10 and notify the Horton lab of the % blast as soon as available (contact info provided below).

Samples must be received by the Horton lab **no later than 72h after collection**. Bone marrow and peripheral blood samples can be batched if they will arrive within 72h. If samples will not arrive within 72h, please send the bone marrow separately from peripheral blood samples. Day 1 peripheral blood samples should be shipped together.

Sample collection time points:

	Baseline	Day 1 Hour 0 (baseline)	Day 1 Hour 6	Day 1 Hour 24
Bone marrow (induction only)[1]	3mL green top[2]			
Peripheral blood (induction only)[3]	5mL in heparin for proteasome assessment[4]	3mL in Cellsave[5] 2mL in heparin[4]	3mL in Cellsave[5] 2mL in heparin[4] (4-6h after start of systemic chemo)	3mL in Cellsave[5] 2mL in heparin[4] (24h after the start of systemic chemotherapy)

** if ixazomib administration is delayed by >18h following start of systemic chemotherapy, collect pre-treatment sample only.

***Sample Collection:**

1. **Bone marrow**: send in heparin or ACDA tube (ACDA preferred). Can also be sent diluted 1:1 in COG shipping media. Do not send bone marrow samples in Cell Save tubes.

2. **Peripheral blood**: Collect 5 mL sample into the CellSave tubes (3 mL) and heparin tubes (2 mL). Either lithium heparin or sodium heparin is acceptable. Do not use PST (plasma separator tubes).

Shipping Note: Samples collected on Saturday and Sunday can be shipped Monday for Tuesday arrival. See below for information on obtaining and shipping samples in ThermoSafe containers.

Specimen Requirements: Store samples in refrigerator until shipment. CellSave tubes will be provided by the Horton lab to each institution upon IRB approval. Please check with your lead CRA to locate the tubes at your institution. To obtain more CellSave tubes, please contact the Horton lab at the numbers provided below. If the CellSave tubes are not available, submit entire 5 mL sample in heparin tubes. Note that the **sample integrity is greatly enhanced by the use of CellSave tubes**.

- Each sample should be clearly labeled to include the TACL registration number as well as the treatment accession number; study number, date and time sample was drawn.
- On the Specimen Transmittal Form record the exact time and date that the sample is drawn along with the exact start time for administration of systemic chemotherapy.
- Please note the WBC and % blasts on the specimen transmittal form.
- The institutional immunophenotype report should be submitted with the Specimen transmittal form. At a minimum we need to know immunophenotype (B-cell or T-cell) status for each sample.

Note: it is acceptable for blood to be collected from a central line.

Shipping Requirements:

Prior to sample collection, please contact Dr. Horton at (832) 824-4269 or Gaye Jenkins/Horton lab at (832) 824-4676 for ThermoSafe shipping containers. ThemoSafe containers maintain biology samples at a constant temperature and are recommended, but not required, for biology sample shipment. Similar boxes are also available in your Pathology Department; boxes used for the shipment of antibodies or FISH probes are also acceptable and will be available more expeditiously than our shipping containers. Shipment of peripheral blood samples should not be delayed for receipt of shipping containers.

If Thermo-Safe shipping container is not available:

- Place collection tubes in a primary container. Wrap each collection tube separately to protect from breakage during shipment. Place the container in a Styrofoam box.
- Please place an **ice pack** in the primary container. During the non-winter months (April-October) add additional ice packs to the Styrofoam box to assure the samples stays cold during shipment. Note that in the South and Southwest, at least 2 ice packs should be used year round.
- Package sample as appropriate for biologic material.

For all samples, including those in ThermoSafe containers: Include a small ice pack in the ThermoSafe container in the space provided.

- Include a copy of the Specimen Transmittal Form with each shipment.
- If possible, please include bone marrow immunophenotype report with the first peripheral blood sample. If this is not possible, please send the report that day via fax (832 825-1206) or email to Dr. Horton at tmhorton@txch.org and Gaye Jenkins at gnjenkin@txch.org (Please strip unnecessary identifiers)
- Ship the sample by Federal Express Priority Overnight delivery to:

Dr. Terzah Horton c/o Gaye Jenkins
Feigin Center, Suite 760.01
1102 Bates St.
Baylor College of Medicine
Houston, TX 77030
832-824-4676

- Notify Gaye Jenkins or Horton lab representative prior to shipment of the sample. Phone: (832) 824-4676 or 832-824-4790. It is acceptable to leave a message if no one is available to answer the phone. Please email the Fed-Ex tracking number to the email addresses above if prior notification is not possible.

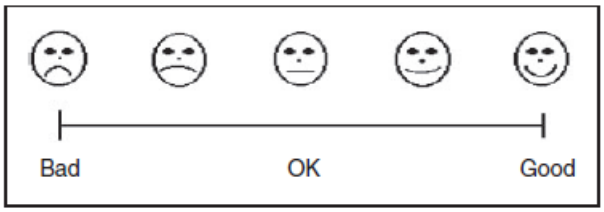
- If possible, do not ship samples for delivery on a weekend or holiday. Please store samples over the weekend if samples are collected on a Friday. Mail on Monday for Tuesday delivery.

APPENDIX VI: PALATABILITY STUDY OF LIQUID ORAL IXAZOMIB (BLOCK 1 ONLY)

TACL Registration #: _____ Date:_____

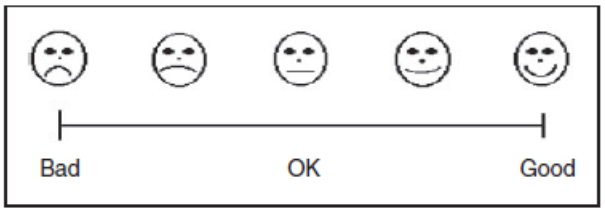
Dose Day: Day 1____ Day 4____ Day 8____ Day 11____
Who Completed the form: Parent/Guardian ____ Child ____

1. What formulation of ixazomib is administered? Capsule ____ Liquid ____
2. Did you (or your child) swallow the dose? Yes_____ No_____
3. What do you think of the taste?



1 2 3 4 5

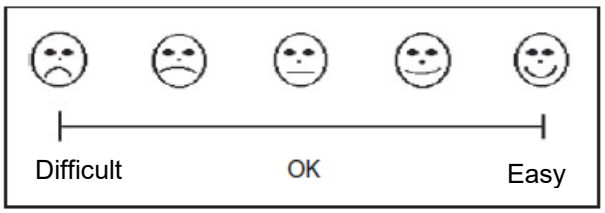
4. What do you think of the smell?



1 2 3 4 5

5. Any aftertaste? Yes____ No____

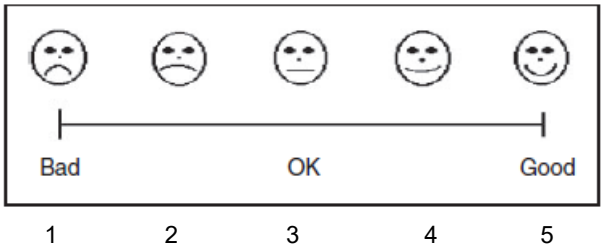
6. How easy is it for you (your child) to take ixazomib?



1 2 3 4 5

7. How easy is it to take other oral medications?

Difficult Easy


Bad
OK
Good
1
2
3
4
5

APPENDIX VII: NEUROLOGICAL EXAM

TACL Registration #: _____ TACL Protocol #: _____

TACL Subject ID : _____ Enrollment Date: _____

Assessment Date: _____

If Pretreatment or Off Study Neurological Exam Section must be completed.

☐ Pretreatment ☐ Dose 1 ☐ Dose 2 ☐ Dose 3 ☐ Dose 4 ☐ Off Study

Neurological Status :

General: ☐ No neurological findings ☐ Improved ☐ Worse ☐ Stable ☐ Resolved

Any Change from baseline: ☐ Yes ☐ No

Any Change from previous assessment: ☐ Yes ☐ No

If Yes, go to Neuro exam; If no to both then assessment is complete.

Neurological Exam:

Mark Normal or Abnormal with an X.
If abnormal, record a brief description of the current abnormality.
Record ND for any examination not done.

	Normal	Abnormal	Description of abnormality
Muscle Tone & Strength: (weakness)			
Reflexes: (, biceps, knee,)			
Gait:			
Cranial Nerves:			
Sensory: (Pain, jaw pain, numbness, paresthesias, constipation,			
Stretch-extension of wrist:			
Stretch-dorsiflexion of foot:			

Comments:

~~Protocol Amendment #1 Version Date: 19December2019~~
~~Protocol Amendment #2 Version Date: 16September2020~~
~~Protocol Amendment #3 Version Date: 11May2021~~
~~Protocol Amendment #4 Version Date: 24January2022~~
~~Protocol Amendment #5 Version Date: 26October2022~~
~~Protocol Amendment #6 Version Date 20July2023~~
Protocol Amendment #7 Version Date: 07September2023

MD Signature Date