Study Protocol and Statistical Analysis Plan

# A phase II study of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) as front-line therapy for adults with acute lymphoblastic leukemia/lymphoma

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# Fred Hutchinson Cancer Center
# University of Washington

# PROTOCOL



## A phase II study of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) as front-line therapy for adults with acute lymphoblastic leukemia/lymphoma

**Protocol Version 2.3**
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# SCHEMA

Registration

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Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin (DA-EPOCH):

Given Approximately Every 21 Days for Up to 8 Cycles

**Cytotoxic Agent Dosing Schema**

| Treatment (Dose Level 1) | Dosing: Days 1-5 of each Cycle[#] | | | | |
|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** |
| Infusional Agents (over ~96 hours) | | | | | |
| Etoposide 50 mg/m$^2$/day* | X | X | X | X | |
| Doxorubicin 10 mg/m$^2$/day* | X | X | X | X | |
| Vincristine 0.4 mg/m$^2$/day | X | X | X | X | |
| Bolus Agents | | | | | |
| Cyclophosphamide 750 mg/m$^2$/day* | | | | | X |
| Prednisone 60 mg/m$^2$/BID[^] | X | X | X | X | X |

[*] Doses of these agents will subsequently increase or decrease by 20% based on the depth of hematologic nadir during the previous cycle, as discussed in Section 7.0.
[^] Conversion to an IV equivalent dose of prednisone is allowable if deemed appropriate by the treating physician
[#] Central nervous system directed therapy with intrathecal/intraventricular methotrexate will also be administered, as discussed in Section 6.3.

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**Non-Cytotoxic Agent Dosing Schema**

- For patients with disease features that predict sensitivity to ABL kinase inhibitors (e.g., Philadelphia Chromosome positive (Ph+) [i.e., t(9;22)]; rearrangements involving *PDGFRA*, *PDGFRB*, *ABL2,* or other genetic lesions that activate kinase receptor signaling): imatinib 600 mg PO daily or dasatinib 100 mg PO daily for 14 days of each 21-day cycle. The decision to add imatinib or dasatinib will be left to the treating physician/PI and will be based on the available scientific literature to support the sensitivity of genomic alterations to these TKIs.

- For CD20+ patients, rituximab 375 mg/m$^2$ IV on Day 1 or 5 of each 21-day cycle
- Myeloid growth factor support: G-CSF ≥ 5 μg/kg SQ daily or PEGylated G-CSF x 1 will be administered after each cycle, starting on Day 6-8.

**TABLE OF CONTENTS:**

# 1.0 OBJECTIVES

## 1.1. Primary Objectives

### 1.1.1. To examine the potential efficacy of DA-EPOCH as front-line therapy for adults with acute lymphoblastic leukemia/lymphoma (ALL)

## 1.2. Secondary Objectives

### 1.2.1. To evaluate the safety and feasibility of this regimen

### 1.2.2. To evaluate the progression-free (PFS) and overall survival (OS) of patients after receiving DA-EPOCH for newly-diagnosed ALL

## 1.3. Exploratory Objectives

### 1.3.1. To explore for novel genetic/genomic biomarkers of prognosis and response to treatment in adults with ALL

### 1.3.2. To compare outcomes predicted by the presence or absence of minimal residual disease (MRD) as determined by either multiparameter flow cytometry (MFC) or high-throughput sequencing (HTS)

# 2.0 BACKGROUND

ALL is among the most common forms of cancer in children, and in this circumstance it is highly curable. However, treatment of ALL in adults is very challenging. Outcomes with standard approaches remain unsatisfactory, with survival rates at 5 years with modern approaches for newly-diagnosed adults generally no better than 50-60%.[1-4] There has been a trend toward using pediatric-inspired regimens in younger (i.e., < 40 years) adults with Philadelphia chromosome negative (Ph-) ALL, with early results from a recent US Intergroup trial (C10403) yielding encouraging results.[5] Despite these and other improvements, however, the treatment still relies primarily upon remission induction with intensive multi-agent cytotoxic chemotherapy. This is a particular challenge in older adults diagnosed with ALL, as these regimens are (in general) prohibitively toxic for these patients.[6] As a consequence of these issues, relapsed/refractory disease is a far-too-common occurrence. And though there is significant enthusiasm for new therapeutic approaches for ALL, including novel immunotherapies and antibody-drug conjugates, these strategies have limited indications or are still in development, and (in some cases) there are significant logistical and/or toxicity concerns.[7-9] Furthermore, these new approaches are not applicable to T-cell ALL. Therefore, continued improvements for the front-line treatment of ALL in adults are critically needed.

ALL, like many other aggressive lymphoid malignancies, is initially quite sensitive to a number of agents, but resistance to these agents develops quite reliably. This argues that an alternative method of delivery of these agents might yield superior outcomes. This was the rationale that led to the development of dose-adjusted EPOCH (etoposide, prednisone, Oncovin [vincristine], cyclophosphamide, and hydroxydaunorubicin [doxorubicin]) for aggressive lymphoma.[10] What makes this approach unique is its infusional nature, providing longer exposure to doxorubicin, vincristine, and etoposide, which is felt to provide better anti-tumor effects than brief, higher-concentration exposure.[11] Indeed, this regimen (along with rituximab) has proven to be highly effective in a number of high-grade lymphoid malignancies, including MYC+ or double-hit B-cell lymphoma and Burkitt lymphoma.[12,13] Further, this regimen is generally

relatively well-tolerated, even in older adults. Thus, it represents an attractive chemotherapy platform to further explore in adults with ALL.

Newer targeted agents have been successfully introduced to the therapeutic landscape of ALL, improving the outcomes for some subgroups of patients. One of the most important developments in the treatment of Ph+ ALL over the past 15 years has been the incorporation of ABL tyrosine kinase inhibitors (TKIs) into treatment regimens.[14-18] The number of agents in this class has grown since the FDA approval of imatinib in 2001, with both dasatinib and ponatinib having been shown to be safe and effective adjuncts to hyperCVAD in newly-diagnosed adults with Ph+ ALL.[15,18] However, there have been no studies that suggest one is superior to another in Ph+ ALL.[17] It is becoming increasingly understood that genetic lesions besides the canonical Philadelphia (Ph) chromosome [*BCR-ABL1*; t(9;22)] may confer a worse prognosis but also may predict response to *ABL* kinase inhibitors like imatinib and dasatinib (e.g., rearrangements involving *PDGFRA*, *PDGFRB*, *ABL2*, etc.). These include the so-called "Philadelphia chromosome-like" or "*BCR-ABL1*-like" ALL.[19] There are also data supporting the safety and efficacy of the anti-CD20 antibody rituximab (when CD20 expression exceeds 20% on the lymphoblasts), including when combined with hyperCVAD and TKI.[18,20,21] Therefore, TKIs and rituximab will also be incorporated into this study of DA-EPOCH to take advantage of their respective impacts on this disease.

Several emerging biomarkers are poised to alter our approach to pre- and post-treatment assessments in ALL. MRD is perhaps the most important prognostic maker in ALL.[22] As polymerase chain reaction (PCR)-based HTS methods have evolved to identify disease-specific clonal sequences in the *IGH* or *TCR* genes, our ability to detect increasingly smaller amounts of residual disease has improved.[23] Small retrospective studies have shown that MRD detection even to this depth may impact risk of subsequent relapse.[23,24] Our hypothesis is that HTS-based MRD detection will identify a greater proportion of patients with persistent disease in either peripheral blood or bone marrow than our center's world-class MFC, and these patients will be at greater risk of subsequent relapse. This trial would be among the first to collect these data prospectively, allowing us to describe the results as well as the practical barriers of incorporating what many feel to be the future of MRD monitoring.

Additionally, new insights into the genetic and genomic landscape of ALL have yielded a better understanding of different biologic subgroups of this disease.[25,26] Chief among these to date is *BCR-ABL1*-like ALL, which is characterized by a similar gene expression profile to *BCR-ABL1*/Ph+ positive ALL, but in the absence of the canonical t(9;22) that characterizes Ph+ ALL. The expression signature is caused by several genetic alterations, including translocations and mutations, which currently must be assayed by combination of FISH and PCR assays. The precise genetic abnormality is important to characterize, as some are targets for tyrosine kinase inhibitors.[19] The incidence in young adults is ≥25% of B-ALL, but little is known about its frequency in older adults. Further, relatively little is known about similar genetic abnormalities in Ph+ ALL or in T-ALL. We will thus use this study as a prospective platform to explore this previously-established subgroup but also novel genetic subtypes of ALL in adults.

## 3.0 DRUG INFORMATION

Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, TKIs (i.e., imatinib, dasatinib), rituximab, and G-CSF must be obtained from commercial sources. Please refer to the current FDA-approved package inserts or the *Physician Desk Reference* for information about possible side effects and instructions for preparation, handling, dosing and storage of these drugs. All study medications will be administered unmodified and unblinded, as described in their respective, approved package inserts.

## 4.0 ELIGIBILITY CRITERIA

### 4.1. Inclusion Criteria

4.1.1. Patients must be ≥ 18 years of age

4.1.2. Patients must have a confirmed diagnosis of either:

- Acute lymphoblastic leukemia
- Lymphoblastic lymphoma with detectable abnormal blasts in the bone marrow

4.1.3. In the opinion of the treating investigator, patients must be an unsuitable candidate for a pediatric-inspired regimen, reasons for which may include (but not be limited to) older age (i.e., ≥ 40 years), practical/logistical barriers to or toxicity concerns from administration of a pediatric-inspired regimen, or Ph+ disease.

4.1.4. Patients must have adequate organ function as defined by the following parameters:

- Total bilirubin ≤ 2.0x institutional upper limit of normal (ULN; unless attributable to Gilbert's disease or other causes of inherited indirect hyperbilirubinemia, at which point total bilirubin must be ≤ 4.0x ULN) and AST (SGOT)/ALT (SGPT) ≤ 5.0x institutional ULN. (Note: Patients with liver test abnormalities attributable to hepatic involvement by ALL will be permitted if the total bilirubin is ≤ 5.0x ULN and ALT/AST are ≤ 8.0x ULN.)
- Creatinine ≤ 2.0 mg/dL; however, patients with a creatinine > 2.0 mg/dL but with a calculated creatinine clearance of > 30 ml/min, as measured by the Modification of Diet in Renal Disease (MDRD) equation, will be eligible.
- As patients with ALL frequently have cytopenias, no hematologic parameters will be required for enrollment or to receive the first cycle of treatment. However, adequate recovery of blood counts will be required to receive subsequent cycles, as defined below.)

4.1.5. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. (Performance status of 3 will be allowed if poor performance status is thought to be directly secondary to ALL.)

4.1.6. Must agree to the use of effective contraception while on study treatment, unless they are highly unlikely to conceive [defined as (1) surgically sterilized, or (2) postmenopausal (i.e., a woman who is > 50 years old or who has not had menses for ≥1 year), or (3) not heterosexually active for the duration of the study].

4.1.7. Ability to give informed consent and comply with the protocol.
4.1.8. Anticipated survival of at least 3 months, independent of ALL.

4.2 Exclusion Criteria

4.2.1 Patients with Burkitt lymphoma/leukemia.
4.2.2 Patients must not have received any prior systemic therapy for ALL, except for the acute management of hyperleukocytosis or acute symptoms (e.g., corticosteroids, cytarabine, etc.)
4.2.3 Patients with isolated extramedullary disease or with known parenchymal central nervous system (CNS) disease.
4.2.4 Known hypersensitivity or intolerance to any of the agents under investigation.
4.2.5 Other medical or psychiatric conditions that in the opinion of the investigator would preclude safe participation in the protocol.
4.2.6 May not be pregnant or nursing.

## 5.0 REGISTRATION

Subjects will be registered by the UW study coordinator and entered into the institutional clinical trials management system. A complete, signed, study consent and HIPAA consent are required for registration.

## 6.0 TREATMENT PLAN

6.1 For treatment or dose-modification related questions, please contact Dr. Cassaday at (206) 606-1202. (MedCon may also be used to contact MDs at 206-543-5300.)

6.2 Treatment will be administered in approximately 21-day cycles (± 3 days) up to 8 total cycles.

Table 1: Administration of DA-EPOCH. Note: This schedule represents a general guideline. Adjustments in the schedule of ± 1 day will be permitted for administrative/scheduling flexibility.

| Drug | Dose | Route | Days | Duration |
|---|---|---|---|---|
| Etoposide* | 50 mg/m$^2$/day | CIV | 1-4 | ~96 hours |
| Doxorubicin* | 10 mg/m$^2$/day | | | |
| Vincristine | 0.4 mg/m$^2$/day (uncapped) | | | |
| Cyclophosphamide* | 750 mg/m$^2$ | IV | 5 | ~1 hour |
| Prednisone$^{\dagger}$ | 60 mg/m$^2$/BID | PO | 1-5 | 5 days |
| Rituximab$^{\#}$ | 375 mg/m$^2$ | IV | 1 or 5 | Per Guidelines |
| TKI: Imatinib^ **OR** Dasatinib^ | 600 mg/day 100 mg/day | PO | 1-14 | 14 days |

| | | | | |
|---|---|---|---|---|
| Filgrastim/TBO-filgrastim[§]<br>**OR**<br>Pegfilgrastim[§] | ~5 mcg/kg/day<br><br>6 mg | SQ<br><br>SQ | Day 6, 7, or 8<br><br>Day 6, 7, or 8 | Daily until ANC > 2000/μL past nadir[∫]<br>Once |
| *Notes* | | | | |
| * Doses of these agents will subsequently increase or decrease by 20% based on the depth of hematologic nadir during the previous cycle, as discussed in Section 7.0.<br>† Conversion to an IV equivalent dose of prednisone is allowable if deemed appropriate by the treating physician<br># Rituximab will be given to patients with CD20+ (defined either qualitatively ["positive," "intermediate," "high," etc.] or quantitatively [≥ 20%]) disease. The rate of infusion and administration of premedications will be according to standard guidelines.<br>^ Delays in initiating this up to the start of Cycle 2 will be permitted to account for time needed to identify the predictive genetic lesion and/or obtain insurance approval for TKI. The choice of imatinib or dasatinib will be left to the discretion of the treating investigator.<br>∫ If ANC ≥ 1000/μL by the start date of the next cycle and the patient is otherwise eligible to proceed with next cycle, daily G-CSF should be discontinued ≥ 24 hours before initiation of next cycle. For patients receiving daily G-CSF, individual doses may be held at the discretion of the treating physician (e.g., for high ANC).<br>§ In the event that a patient starts daily G-CSF but is unable to continue until recovery (e.g., intolerant of daily injections, financial issues, etc.), a single dose of pegfilgrastim may be given as a substitute, provided it is given no later than Day 8 of the chemotherapy cycle.<br>Abbreviations: ANC = absolute neutrophil count; CIV = continuous intravenous infusion; IV = intravenous; PO = by mouth; SQ = subcutaneous | | | | |

6.3 CNS-Directed Therapy

6.3.1 As CNS prophylaxis is a standard part of treating ALL, all patients should receive intra-CSF chemotherapy either via lumbar puncture (intrathecal [IT]) or Ommaya reservoir.

6.3.2 For patients with active CNS disease at the time of enrollment or unable to undergo multiple lumbar punctures, placement of an Ommaya reservoir and consultation/co-management with Neuro-Oncology will be strongly encouraged.

6.3.3. The details regarding the dosing and timing of intra-CSF chemotherapy will not be stipulated by this protocol. Instead, this will be left to the discretion of the treating investigator. That said, the following is a recommendation, based on prior experience with DA-EPOCH in adults with Burkitt lymphoma[12]:

6.3.3.1 If CNS negative at screening, methotrexate 12 mg IT or 6 mg intra-Ommaya on Days 1 and 5 of each chemotherapy cycle beginning with cycle 1 for 8 total doses. For patients with a high white blood cell count and/or LDH at diagnosis, consider increasing to 10 total doses.

6.3.3.2 If CNS positive at screening, methotrexate 12 mg IT or 6 mg intra-Ommaya twice weekly for 4 weeks, then once weekly for 6 weeks, then once monthly for 4 months.

6.4 Supportive Care

6.4.1 Nausea/vomiting prophylaxis: Antiemetic prophylaxis is recommended during administration of EPOCH chemotherapy on Days 1-5, at the discretion of the treating investigator. Other antiemetics (e.g., lorazepam, promethazine, etc.) should be prescribed according to the discretion of the prescribing physician.

6.4.2 Infection prophylaxis: Gram negative bacterial prophylaxis (e.g., levofloxacin) is highly recommended once a patient's absolute neutrophil count (ANC) is $\leq$ 1,000 cells/μL. Herpes virus prophylaxis (e.g., acyclovir) and *Pneumocystis* prophylaxis (e.g., trimethoprim-sulfamethoxazole) are also strongly recommended during protocol treatment.

6.4.3 Tumor lysis syndrome (TLS) prophylaxis/treatment: TLS is a relatively common complication of treating ALL. Active prevention and treatment of TLS with hypouricemic agents and/or aggressive IV hydration is highly recommended during the first cycle of study treatment. The details of this will be left to the discretion of the treating investigator based on individual patient risk factors.

6.4.4 Monitoring for consumptive coagulopathy/disseminated intravascular coagulation (DIC): DIC can be observed during the treatment of ALL. Laboratory monitoring and management of abnormal laboratory parameters, including clotting factor replacement, will be left to the discretion of the treating physician based on individual patient risk factors.

6.4.5 Miscellaneous: Treatment can be administered on either an inpatient or outpatient basis. However, it is required that cycle 1 be administered while inpatient for the first 5-6 days, per the usual care with these drugs, to monitor for early toxicities. The remaining days of Cycle 1 may be administered either inpatient or outpatient, based on treating physician decision. Concurrent IV hydration during the infusional portion of EPOCH should be strongly considered, particularly in patients who are not considered able to maintain sufficient oral hydration to generate adequate urine output; details of this will be deferred to treating physicians.

6.5 Post-Protocol Therapy

6.5.1 Allogeneic HCT: Patients that are deemed to be appropriate candidates may proceed to HCT at the discretion of the treating investigator. However, patients should receive $\geq$ 2 cycles of study therapy to adequately assess toxicity and response before being referred for HCT. Following HCT, patients will be followed only for survival and relapse/progression of disease.

6.5.2 Maintenance Therapy: For patients who are not referred for HCT, maintenance therapy will be highly encouraged, as is routinely offered to patients with ALL. The specifics of maintenance therapy will be left to the discretion of the treating investigator, but ideally should include monthly cycles

of vincristine and a corticosteroid (plus TKI if disease characteristics at diagnosis predict sensitivity, such as Ph+, *PDGFRA*, *PDGFRB*, *ABL2*, etc.) and should be continued for approximately 2 years. Maintenance therapy should only be considered after patients have received ≥ 2 cycles of study therapy to adequately assess toxicity and response. Following initiation of maintenance therapy, patients will be followed only for survival and relapse/progression of disease.

6.5.3 Radiation Therapy: Patients may receive consolidative radiation therapy (e.g., mediastinal mass, testicular involvement, additional CNS-directed therapy) at the discretion of the treating physician. However, this should only be considered after patients have received ≥ 2 cycles of study therapy to adequately assess toxicity and response. Furthermore, study treatment with DA-EPOCH will NOT resume once radiation therapy has commenced.

6.6 Patients will be assessed for response as specified in section 9.0. Criteria for removal from protocol treatment are as follows:

6.6.1 Treatment failure, which will be defined as any of the following:

6.6.1.1 Documented progression/relapse of disease.

6.6.1.2 Inadequate response, as defined by any of the criteria below:

- Persistent morphologic disease after 2 cycles of treatment
- Progressive/refractory disease by imaging as defined in section 9.3.5.2
- MRD persistence after 6 cycles of treatment

6.6.2 Any related grade 4 non-hematologic toxicity (excluding asymptomatic laboratory abnormalities).

6.6.3 Development of any unacceptable toxicities unless prophylactic measures can be taken for subsequent cycles.

6.6.4 Delay of treatment for more than 3 weeks due to adverse events.

6.6.5 Completion of protocol treatment (maximum of 8 cycles or patient/investigator preference to refer for HCT or begin maintenance therapy).

6.6.6 If none of the above criteria are explicitly met but a change in treatment is felt to be appropriate, patients may be removed from protocol treatment at the discretion of the treating physician.

6.6.7 The patient may withdraw from the treatment at any time for any reason.

## 7.0 DOSAGE MODIFICATIONS

Standard dose adjustments for etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and TKIs may be made based on changes in hepatic and renal function during treatment. The following parameters for retreatment and treatment modifications are suggested; however, these represent general guidelines and can be adjusted based on the discretion of the treating physician and PI.

### 7.1 Modifications for Hematologic Toxicity

7.1.1 Subsequent cycles of therapy will not begin until the ANC is ≥ 1000/μL and the platelet count is ≥ 50,000/μL.

7.1.1.1 Therapy will be delayed a maximum of 3 weeks until these values are achieved. Patients who fail to recover adequate counts within 3 weeks will be removed from study treatment.

7.1.1.2 If the ANC and platelet counts have recovered to these thresholds and the investigator feels it beneficial, patients will be given the option to admit for the next cycle earlier than the 21-day mark, provided the start of the next cycle is ≥ 14 days since the start of the previous cycle and enough time is allowed to complete any necessary assessments of toxicity and/or response.

7.1.2 Beginning with cycle 2, the doses of etoposide, doxorubicin, and cyclophosphamide will be adjusted based on the depth of the hematologic nadir from the preceding cycle.[10]

7.1.2.1 If ANC nadir ≥ 500/μL, increase doses by 1 dose level above last cycle

7.1.2.2 If ANC nadir < 500/μL on 1 or 2 measurements, maintain the same dose level as last cycle

7.1.2.3 If ANC nadir < 500/μL on ≥ 3 measurements, OR if platelet nadir < 25,000/μL at any time, decrease doses by 1 dose level below last cycle.

Table 2: Drug doses per dose levels

| Drugs | -2 | -1 | 1 "starting dose" | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|
| Doxorubicin ($mg/m^2/day$) | 10 | 10 | 10 | 12 | 14.4 | 17.3 | 20.7 | 24.8 |
| Etoposide ($mg/m^2/day$) | 50 | 50 | 50 | 60 | 72 | 86.4 | 103.7 | 124.4 |
| Cyclophosphamide ($mg/m^2/day$) | 480 | 600 | 750 | 900 | 1080 | 1296 | 1555 | 1866 |

For the purposes of this protocol, this range of dose levels is not absolute. Decreasing below Dose Level -2 or above Dose Level 6 will be permitted based on the discretion of the treating physician. Further, if the depth of the nadir would necessitate a decrease below Level -2 or above Level 6, these dose levels can be maintained if a patient is deriving benefit from this chemotherapy regimen. This provides an alternative option beyond further adjustment outside this range or removal from the protocol.

Adjustments will be made based on results of complete blood counts (CBCs) checked approximately 3 days apart, +/- 1 day for logistical/administrative flexibility. If patients undergo more frequent laboratory monitoring for routine clinical purposes, only labs that meet this definition will be used for dose-adjustment purposes. For example,

if a patient has a CBC checked daily, the results from only Monday and Thursday or Tuesday and Friday will be considered. Dose re-escalation will be permitted if the above criteria are met following a dose reduction.

In the event that a patient has significant cytopenias that are felt to be primarily due to marrow involvement by ALL, dose reductions for the subsequent cycle should NOT be performed unless there is a > 7-day delay to adequate hematologic recovery to begin the subsequent cycle or unless a dose reduction is felt to be medically appropriate at the discretion of the treating physician. Based on the study design, this will primarily impact dosing for Cycle 2, as patients with extensive marrow involvement after 2 cycles of treatment will not likely be eligible to continue to Cycle 3 (see Section 6.6 above).

7.2 Modifications for Impaired Renal Function

7.2.1 Serum creatinine must be < 2.0 mg/dl or an *estimated* or measured creatinine clearance must be > 30 ml/minute by the MDRD equation on Day 1 of each cycle (lab may be drawn up to 3 days prior to day 1). If these values are not met, treatment may be delayed for up to 3 weeks. If these values do not recover within 3 weeks, the patient will be removed from protocol treatment.

7.3 Modifications for Impaired Liver Function

7.3.1 Total bilirubin must be < 2.0x ULN (or < 4.0x ULN for patients with Gilbert's disease or other causes of inherited indirect hyperbilirubinemia), and ALT/AST < 5.0x ULN on Day 1 of each cycle (lab may be drawn up to 3 days prior to day 1). If these values are not met, treatment may be delayed for up to 3 weeks. If these values do not recover within 3 weeks, the patient will be removed from protocol treatment.

7.4 Modifications for Rituximab-Associated Toxicities

7.4.1 For patients who receive rituximab and experience grade 3 or higher infusion related reactions, subsequent doses of rituximab may be omitted at the discretion of the treating investigator

7.4.2 Patients in whom this occurred may remain on study, receiving treatment without rituximab, provided other rules governing treatment delays, etc. are met.

7.5 Modifications for TKI-Associated Toxicities

7.5.1 The following instructions represent recommendations for treating physicians; deviations from these instructions are permissible at the discretion of the treating investigator.

7.5.2 If a patient receiving TKI experiences hematologic toxicity requiring dose reduction of etoposide, doxorubicin, and cyclophosphamide on 2

consecutive cycles, the dose of TKI for that patient can be reduced: if on imatinib, the dose can be reduced to 400 mg PO daily on Days 1-14 of all subsequent cycles; if on dasatinib, the dose can be reduced to 70 mg PO daily on Days 1-14. If a dose reduction of etoposide, doxorubicin, and cyclophosphamide is required for a 3rd consecutive cycle, then the dose of TKI can be reduced again for all subsequent cycles: for imatinib, 200 mg PO daily on Days 1-14; for dasatinib, 50 mg PO daily on Days 1-14. If this issue persists, contact the Study Chair to discuss further dose adjustments.

7.5.3 For non-hematologic toxicity attributable to TKI (e.g., diarrhea, edema):

7.5.3.1 If moderate (i.e., Grade 2) and unable to be controlled with additional supportive care, therapy may continue but with the dose reduced (imatinib 400 mg PO daily or dasatinib 70 mg PO daily on Days 1-14). If symptoms do not improve to Grade 1 or less, further reduction can occur (imatinib 200 mg PO daily or dasatinib 50 mg PO daily on Days 1-14). If the issue persists, contact the Study Chair to discuss further dose adjustments.

7.5.3.2 If severe (i.e., Grade 3), TKI can be held until symptoms attributable to the event have improved and/or severity has resolved to Grade 1 or less, then resumed at a reduced dose (imatinib 400 mg PO daily or dasatinib 70 mg PO daily on Days 1-14). If the same Grade 3 event recurs at the reduced dose, TKI can again be held and resumed as above, but reduced further (imatinib 200 mg PO daily or dasatinib 50 mg daily on Days 1-14). If the issue persists, contact the Study Chair to discuss further dose adjustments.

7.5.3.3 If life-threatening (i.e., Grade 4), TKI can be discontinued.

7.5.4 Additionally, TKI may be discontinued at the discretion of the treating investigator in the event of any other clinically-significant adverse event attributable to this drug that is unlikely to recur or worsen with discontinuation of the drug

7.5.5 For patients who experience toxicities as above that warrant dose-reduction or discontinuation of the initial TKI used, they may be switched to an alternative TKI at the discretion of the treating investigator.

7.5.6 Patients in whom TKI has been stopped may remain on study, receiving treatment without TKI, provided other rules governing treatment delays, etc. are met.

7.6 Modifications for Other Adverse Events

7.6.1 Except for those drug-specific events described above, any other grade 4 non-hematologic toxicity possibly, probably or definitely related to the drug combination (excluding asymptomatic laboratory abnormalities) as defined in Section 10 will result in the patient being removed from protocol treatment.

7.6.2 Patients should receive appropriate medical management for adverse events. Treatment may be delayed up to 3 weeks for clinically significant grade 2 or 3 adverse events and unrelated grade 4 adverse events at the discretion of the treating physician. If treatment is delayed for 3 weeks, the patient will be removed from protocol treatment.

7.7 Concomitant Therapy

7.7.1 *Prohibited Concomitant Therapy:* The administration of concurrent medications intended to treat the primary cancer is not allowed during protocol therapy. This includes any chemotherapy, investigational agent, biologic agent or other anti-tumor agents. Concomitant radiation therapy is also prohibited, though it is permitted as post-protocol therapy as per Section 6.5.3. CNS directed chemotherapy per section 6.3 is allowed.

7.7.2 Patients should be strongly discouraged from taking any “alternative” or “naturopathic” medications since these agents may interact with study treatment. Any use of these medications should be at the judgment of the treating investigator and should be documented in the patient’s medical record.

## 8.0 STUDY CALENDAR (Table 3)

| Required Studies | Pre-Entry[1] | Within 3 Days Prior to Each Cycle[7] | Monitoring Between Cycles: ≥ 2x/Week[8] | Interim Response Assessment[9] | Post Therapy[11] | Follow-up[12] |
|---|---|---|---|---|---|---|
| **Physical** | | | | | | |
| History and Physical | X* | X[7] | | | X[11] | X[12] |
| Performance Status | X | X[7] | | | X[11] | |
| Clinical Disease Assessment | X | X[7] | | | X[11] | |
| Adverse Event Assessment | Adverse Events will be continuously monitored from time of consent to 30 days post discontinuation of all study treatment, or until the patient receives an alternative anti-cancer therapy, whichever date comes first. Treatment related toxicities last > 30 days will be followed until a satisfactory resolution has been achieved. | | | | | |
| | | | | | | |
| **Laboratory Assessments** | | | | | | |
| CBC, Diff, platelets | X[7] | X[7] | | | X[11] | X[12] |
| CBC, ANC, platelets | | | X[8] | | | |
| Creatinine, electrolytes, glucose, total bilirubin, ALT, AST, alk phos, LDH, albumin | X | X[7] | | | X[11] | |
| Pregnancy test | X[2] | | | | | |
| Bone Marrow Studies | X[3,4] | | | X[3,9] | X[3,11] | |
| **Radiology** | | | | | | |
| CT Chest, abdomen and pelvis; CT neck if cervical adenopathy present | X[5] | | | X[5,9] | X[5,11] | |
| **Correlative Studies** | | | | | | |
| Peripheral Blood | X[6] | | | | | |
| Bone Marrow | X[6] | | | X[10] | X[10,11] | |

* Height will be assessed once at the pre-entry visit

[1] Pre-entry studies should be obtained ≤ 2 weeks from enrollment, unless otherwise indicated by protocol or provider.

[2] Pregnancy test is only required in women, unless they are highly unlikely to conceive [defined as (1) surgically sterilized, or (2) postmenopausal (i.e., a woman who is > 50 years old or who has not had menses for ≥1 year), or (3) not heterosexually active].
[3] Bone marrow studies should include unilateral aspirate or (if inaspirable) biopsy. All bone marrow samples should be sent for morphology, flow cytometry, and (for Ph+ patients) BCR-ABL quantitative PCR; additional studies (e.g., based on known molecular or cytogenetic abnormalities) may be performed at the discretion of the treating investigator. In cases where a genetic abnormality is identified that predicts response to TKIs, imatinib or dasatinib will be added at the discretion of the PI and/or treating physician based on the specific genetic lesion identified and the available scientific literature to support sensitivity to these TKIs. These results should be obtained from clinically/commercially-available assays performed in a CAP/CLIA-certified laboratory. In general, these assays utilize either FISH or RT-PCR based methods to identify specific gene fusions. As the turnaround time can exceed one week, enrollment will not be dictated by these results; they will only be acted upon in the event that they become available after study treatment has commenced.
[4] Pre-entry bone marrow exam may be omitted in patients with circulating leukemia in the peripheral blood in adequate amounts to perform flow cytometry and routine cytogenetics.
[5] Imaging studies should be performed only if extramedullary disease is suspected. While CT-based imaging is preferred, other imaging studies will be leveraged if performed for clinical reasons and they provide sufficient description of disease status for response-assessment purposes.
[6] For patients with a sufficient amount of circulating leukemia, necessary samples for pre-entry correlative studies will be obtained via peripheral blood draw. Alternatively, we may attempt to obtain adequate material from the bone marrow studies performed for clinical purposes to establish the diagnosis (either freshly obtained or archived material).
[7] For Cycle 1 Day 1, pre-entry H&P, performance status, laboratory studies, disease assessment and adverse event assessment may be used (i.e., these do not need to be repeated within 3 days). CBC with differential should be performed within three days of subsequent cycle starts.
[8] These represent recommended laboratory monitoring guidelines between cycles of treatment for the purposes of dose adjustments of etoposide, doxorubicin, and cyclophosphamide (Section 7.1.2); more frequent monitoring should be considered on an individual patient basis at the discretion of the treating physician. Once hematologic recovery from the prior cycle of chemotherapy is observed, laboratory monitoring can be reduced in frequency at the discretion of the treating physician.
[9] Bone marrow response will be assessed prior to Cycle 2 and repeated (if necessary) no less often than after every 3 subsequent cycles until either a complete MRD response or progressive disease (PD) is observed, or study treatment is completed. For patients with persistent disease by bone marrow morphology after Cycle 1, a bone marrow exam must be repeated after Cycle 2, as persistent morphologic disease after 2 cycles will lead to discontinuation of study therapy. For patients who achieve a complete MRD response, subsequent interim-response bone marrow assessments should be performed again between 2-4 calendar months of documentation of complete MRD response to confirm persistence of response. Patients with PD based on imaging or a rising peripheral lymphoblast count may forego a bone marrow exam. For patients with measurable extramedullary disease on the "pre-entry" CT, an interim response CT is recommended at some point between the start of cycles 2 and 5, particularly for patients deemed by the treating physician to have a significant burden of extramedullary disease at enrollment.
[10] Concurrently with the bone marrow samples obtained for clinical response assessment (e.g., prior to Cycle 2, end of treatment, and an intermediate assessment [e.g., prior to Cycle 5]), material will be collected for HTS-based MRD detection.
[11] Post therapy studies should be done at least 3 weeks after the start of the patient's last cycle of study therapy, unless otherwise specified. Post-therapy CT may be omitted in patients without extramedullary disease at enrollment. For patients with a significant burden of extramedullary disease by CT at enrollment, PET/CT is recommended to confirm CR.
[12] The timing of follow-up visits will not be explicitly stated. A recommended schedule is every 3 months for 2 years then every 6 months for 3 years (total follow-up time 5 years). These visits may be performed by outside physicians, provided medical records documenting patient status are available. Furthermore, the specific assessments performed at these visits will not be required by the protocol: history, physical examination, and CBC with diff and platelets are the minimum RECOMMENDED assessments; bone marrow studies are NOT REQUIRED. For the purposes of data collection, patients will be followed for up to 5 years after enrollment for subsequent therapy, relapse, and survival.

## 9.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Definitions of Disease, Criteria for Evaluation and Endpoint Definitions – bone marrow response will be defined by standard morphologic and MRD criteria for acute leukemia,[27,28] while sites of extramedullary disease will be assessed according to the National Comprehensive Cancer Network (NCCN) response criteria.[29] Response assessments via imaging will be taken from clinical reports. While CT ± PET are the preferred imaging modalities, these same principles will be applied to results of other imaging studies used if the clinical situation warrants their use in specific circumstances.

For the purposes of study eligibility, evaluable disease will be defined as positive bone marrow morphology or MRD assessment (as defined below). Patients will be considered evaluable for the primary objective of the study if they complete 4 cycles of study treatment, or one of the following occurs: (1) complete MRD response is documented prior to the end of cycle 4, (2) removal from protocol treatment prior to completing 4 cycles for any of the criteria listed in Section 6.6 EXCEPT 6.6.7, or (3) death from any cause prior to completing 4 cycles. Patients who discontinue protocol treatment before completing 4 cycles for other reasons (e.g., unable to continue receiving treatment at our center, withdrawal of consent, etc.) will not be considered evaluable. Data will still be collected from these patients as available and as circumstances allow to address secondary study objectives.

9.1 Bone Marrow Status: Bone marrow status is evaluated as follows:

- 9.1.1 Positive by morphology: ≥ 5% blasts
- 9.1.2 Negative by morphology: < 5% blasts
  - 9.1.2.1 MRD positive: negative by morphology but detectable disease using more sensitive assays (e.g., MFC)
  - 9.1.2.2 MRD negative: negative by morphology and MFC. *(Note: For patients who have genetic abnormalities that can be measured by quantitative PCR (e.g.,* BCR-ABL1*), MRD status will be assessed by PCR if available, in addition to MFC. These results may be used clinically at the discretion of the treating physician, but they will not contribute to the primary endpoint of the study to allow for a more consistent assessment of MRD across all patients via MFC.)*

9.2 Measurability of Extramedullary Lesions:

- 9.2.1 Measurable Disease: Lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), plain x-ray, or other conventional technique and a greatest transverse diameter of 1.5 cm or greater; or palpable lesions with both diameters ≥ 2 cm. Note: CT scans remain the standard for evaluation of nodal disease.

9.2.2 Non-measurable Disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, lymphangitis, pneumonitis, abdominal masses not confirmed or followed by imaging techniques, or disease documented by indirect evidence only (e.g., lab values).

9.3 Objective Disease Status: Objective status is to be recorded at each evaluation. As patients may have evaluable disease by bone marrow evaluation, imaging, or both, response definitions for bone marrow will supersede those for extramedullary disease unless imaging demonstrates progressive/refractory disease, as defined below.

9.3.1 Complete Response (CR):

9.3.1.1 Bone Marrow: < 5% blasts by morphology, ANC > 1000/μL, platelets > 100,000/μL

9.3.1.1.1 CR with incomplete hematologic recovery (CRi): < 5% blasts by morphology but either ANC < 1000/μL or platelets < 100,000/μL

9.3.1.1.2 Complete MRD response: morphologic CR/CRi and no detectable disease by MFC

9.3.1.1.3 MRD persistence: morphologic CR/CRi but detectable disease using MFC

9.3.1.2 Imaging: Complete resolution of lymphomatous enlargement. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.

9.3.2 Partial Response (PR):

9.3.2.1 Bone Marrow: Decrease of at least 50% in the proportion of blasts by morphology to 5-25% of the total marrow cellularity, ANC > 1000/μL, platelets > 100,000/μL

9.3.2.2 Imaging: >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the lymphomatous enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

9.3.3 Stable disease (SD): Does not qualify for CR, PR, or Relapsed/Progressive Disease. All disease must be assessed using the same technique as baseline.

9.3.4 Relapsed Disease:

9.3.4.1 Bone Marrow: Re-appearance of > 5% blasts by morphology after having previously achieved a CR.

9.3.4.1.1 MRD reappearance: Conversion to MRD positivity after having previously met the criteria to be defined as MRD negative.

9.3.4.2 Imaging: Recurrence of the lymphomatous enlargement after achieving CR. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

9.3.5 Progressive/Refractory Disease (PD):

9.3.5.1 Bone Marrow: Survival ≥ 7 days after completion of study treatment with disease present by morphology in the most recent bone marrow evaluation.

9.3.5.2 Imaging: >25% increase in the SPD of the lymphomatous enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

9.3.6 Assessment inadequate, objective status unknown: Progression has not been documented and one or more target lesions or other sites of disease have not been assessed or inconsistent methods of assessment were used.

## 10.0 STATISTICAL CONSIDERATIONS

10.1 Primary Objective: To examine the potential efficacy of DA-EPOCH as front-line therapy for adults with ALL

Efficacy will be examined by evaluating the response rates in two subgroups, independent of each other: Ph+ patients and Ph- patients. As our eligibility criteria will relatively enrich for Ph+ patients, enrollment into this subgroup is expected to be higher. We will attempt to take advantage of this by implementing a statistical design to more precisely estimate the response rate in Ph+ ALL. This will also help place our results into a clearer context of other, lower-intensity strategies for Ph+ ALL which have emerged.[30,31] Alternatively, the design used for the Ph- subgroup will be less statistically rigorous, intended more to ensure that DA-EPOCH is not clearly inferior to a historical standard.

If either group closes due to the efficacy stopping rules outlined below (see sections 10.1.1 and 10.1.2), the other group may continue to enroll patients, provided it has not met its protocol-defined efficacy stopping rule. The stopping rules for safety (see section 10.4.2) will be applied to both Ph+ and Ph- subgroups in aggregate. Patients that lack t(9;22) but receive a TKI for *BCR-ABL1*-like ALL will be evaluated in the Ph- group; it is not known if TKIs augment the efficacy of chemotherapy to the same degree in this subgroup of patients.[19]

10.1.1 Efficacy in Ph+ Patients

For newly-diagnosed adults with ALL, the probability of achieving a complete MRD response by MFC within 90 days of initiation of hyperCVAD at our institution is 50%.[32] We will consider DA-EPOCH successful in Ph+ patients if we observe a complete MRD response rate by MFC after 4 cycles (i.e.,

approximately 90 days) of at least 70%. A Simon two-stage minimax design will be used to assess the potential efficacy of this treatment. After 15 patients have been enrolled, if 7 or fewer responses (47% or less) have been observed the study will be placed on an enrollment hold to review potential corrective actions for lack of sufficient efficacy. The probability of this occurrence is 0.50 if the true response rate is 50%. If 8 or more responses are seen among the first 15 patients, enrollment will continue until 28 patients, at which point the study will be considered to be potentially efficacious if at least 18 responses are seen among the 28 patients (64% or higher estimated response rate). The expected number of patients to be enrolled under this design and these assumptions is 21.5, and the type I error rate is 0.09 and the power is 80%.

10.1.2 Efficacy in Ph- Patients

The historical rate of complete MRD response by MFC within 90 days (i.e., after 4 cycles) for Ph- patients receiving hyperCVAD is 59%.[32] For Ph- patients who receive DA-EPOCH, we will calculate the rate of complete MRD responses after the first 10 patients, then again in cohorts of 5 patients. We will determine a 90% confidence interval of the response rate for each of these cohorts. As long as the upper bound of this confidence interval is not < 59% (which would indicate a high probability that DA-EPOCH is in fact less effective than hyperCVAD), we will continue to enroll up to a maximum of 25 patients. This would mean we would need to see complete MRD responses at the following rates to continue enrollment into this cohort: ≥ 4 of the first 10 patients, ≥ 6 of the first 15 patients, and ≥ 9 of the first 20 patients.

10.2 Secondary Objectives

Reporting of secondary objectives will be primarily descriptive, with comparisons using established statistical methods. Binary outcomes will be estimated with proportions and associated confidence intervals, time-to-event outcomes will be estimated using Kaplan-Meier or cumulative incidence estimates, as appropriate. Although the sample size will be small, outcomes will be compared between those with and those without MRD. The chi-square test (or Fisher's exact test) will be used for binary outcomes; the log-rank test will be used for time-to-event outcomes. More emphasis will be placed on the magnitude of differences rather than the resultant p-values from these comparisons, and the estimated effects will be used in the design of subsequent studies.

10.2.1 To evaluate the safety and feasibility of this regimen

To quantify this, the following events will be noted:

- Any non-hematologic grade 3 or higher NCI CTCAE adverse event (excluding asymptomatic grade 3 laboratory abnormalities) that is possibly, probably or definitely related to the drug combination until 30 days after discontinuation of all study treatment or the start of an alternative therapy.

- Any patients that do not complete one full cycle of therapy due to toxicity from the treatment. Patients choosing to stop study medication for adverse events that are not considered medically significant by the Investigator will not be included.
- Any serious adverse event that is possibly, probably or definitely related to the drug combination, but does not meet the above criteria.

10.2.2 To evaluate the PFS and OS of patients after receiving DA-EPOCH for newly-diagnosed ALL

10.3 Exploratory Objectives

Reporting of exploratory objectives will be primarily descriptive, with comparisons using established statistical methods. Binary outcomes will be estimated with proportions and associated confidence intervals, time-to-event outcomes will be estimated using Kaplan-Meier or cumulative incidence estimates, as appropriate. Although the sample size will be small, outcomes will be compared between those with and those without MRD. The chi-square test (or Fisher's exact test) will be used for binary outcomes; the log-rank test will be used for time-to-event outcomes. More emphasis will be placed on the magnitude of differences rather than the resultant p-values from these comparisons, and the estimated effects will be used in the design of subsequent studies.

10.3.1 To explore for novel genetic/genomic biomarkers of prognosis and response to treatment in adults with ALL

10.3.2 To compare outcomes predicted by the presence or absence of MRD as determined by either MFC or HTS

10.4 Anticipated accrual: Based on the design above, we will enroll up to 53 patients. Patients who enroll and receive study treatment but do not meet the definition of "evaluable for the primary objective" as outlined in Section 9.0 will not count toward the enrollment goals and will be replaced.

10.5 Stopping Rules: Patients will not be enrolled until adequate follow-up is available to satisfy these rules. The Principal Investigator is responsible for reviewing patient data in real-time to ensure adherence to these stopping rules.

10.5.1 To limit the number of patients exposed to a potentially-ineffective therapy, the study will be placed on an enrollment hold to review potential corrective actions for futility as detailed above. Moreover, the study will pause prior to enrolling 15 patients (the first stage of the minimax design) if 8 responses are not possible among the first 15 patients (e.g., if no responses occur within the first 8 patients).

10.5.1.1 For those who do not achieve a complete MRD response with DA-EPOCH, it is worth emphasizing that outcomes incorporating HCT after complete MRD response following subsequent/salvage therapy are comparable to HCT while in first complete MRD remission for ALL.[33] For those subjects who do not achieve a complete MRD response to DA-EPOCH, second-line therapy (with hyperCVAD or others) shall be given with this goal in mind.

10.5.2 The study will be placed on an enrollment hold to review potential corrective actions for safety using 2 different rules, based on recent published experience with hyperCVAD.[15,18] These will be assessed in cohorts of 5 patients:

10.5.2.1The lower bound of the 80% confidence interval of the incidence of grade 3 or higher non-hematologic toxicity occurring during the first 2 cycles of treatment possibly, probably or definitely related to the drug combination (excluding neutropenic fever and asymptomatic Grade 3 laboratory abnormalities) exceeds 60%. Thus, this rule would be enacted if 5 of the first 5 patients, ≥ 8 of the first 10 patients, ≥ 12 of the first 15 patients, ≥ 15 of the first 20 patients, ≥ 18 of the first 25 patients, ≥ 22 of the first 30 patients, ≥ 25 of the first 35 patients, ≥ 28 of the first 40 patients, ≥ 31 of the first 45 patients, or ≥ 35 of the first 50 patients experience such an event.

10.5.2.2. The lower bound of the 80% confidence interval of the incidence of treatment-related death exceeds 10%. Thus, this rule would be enacted if ≥ 2 of the first 5 patients, ≥ 3 of the first 10 patients, ≥ 3 of the first 15 patients, ≥ 4 of the first 20 patients, ≥ 5 of the first 25 patients, ≥ 6 of the first 30 patients, ≥ 7 of the first 35 patients, ≥ 8 of the first 40 patients, ≥ 8 of the first 45 patients, or ≥ 9 of the first 50 patients experience such an event

10.6 Estimated distribution of study population by gender and race and ethnicity (Table 4):

| **Ethnic Category** | Females | Males |
|---|---|---|
| American Indian/Alaska Native | | 1 |
| Asian | 2 | 1 |
| Native Hawaiian or Other Pacific Islander | | |
| Black or African American | 1 | 2 |
| White | 16 | 16 |
| Hispanic or Latino | 7 | 7 |
| More than one race | | |
| Unknown or not reported | | |
| **Racial Categories: Total of all subjects** | 26 | 27 |

## 11.0 STUDY MONITORING AND REPORTING PROCEDURES

## 11.1 Adverse Event Reporting

AEs of Grade 3 and above, and Serious Adverse Events (SAEs) occurring at any grade will be monitored and recorded in study-specific case report forms (CRFs) from the time the patient signs consent through 30 days following discontinuation of study treatment, or until the patient receives an alternative anti-cancer therapy, whichever date comes first. Treatment related toxicities will be followed until a satisfactory resolution has been achieved. AEs related to biopsies that are done solely for research study screening purposes will be monitored, recorded, and reported according to the same standards, with the exception that assessment of study drug attribution will be excluded from reporting criteria.

The NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE) will be used to classify and grade toxicities. The CTC can be found on the Cancer Therapy Evaluation Program (CTEP) homepage at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

## 11.2 Definitions and descriptions of terms used in adverse event reporting.

***Adverse Event (AE)***
An AE is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

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

***Serious Adverse Event (SAE) or Adverse Drug Reaction (ADR)***
A *Serious Adverse Event* or *Adverse Drug Reaction* means any AE/ADR occurring at any dose that results in:

- Death;
- A life-threatening AE/ADR (i.e., the patient/subject was, in the view of the initial reporter/investigators, at immediate risk of death from the AE as it occurred. It does not refer to an AE that hypothetically might have caused death if more severe);

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- Inpatient hospitalization or prolongation of existing hospitalization (Hospitalization itself will not be considered a serious adverse event if required for complications of ALL or comorbid conditions.

Hospitalization will be considered an SAE if it fulfills the criteria for a serious and unexpected adverse event as otherwise described);

- A persistent or significant disability or incapacity (disability here means that there is a substantial disruption of a person's ability to conduct normal life functions);

- A congenital anomaly/birth defect;

- An important medical event (i.e., AEs/ADRs that might not be immediately life-threatening, or result in death or hospitalization might be considered serious when, based upon appropriate medical and scientific judgment, they might jeopardize the patient/subject or might require medical or surgical intervention to prevent one of the other serious outcomes listed above);

- Any suspected transmission via a medicinal product of an infectious agent.

Investigator shall use his/her judgment to determine the relationship between the Serious Adverse Drug Experience and the Study Drug.

***Grade***

*Grade* is defined as the severity of the adverse event. The CTCAE Version 5.0 must be used to determine the grade of the adverse event. If toxicity is not listed in the CTCAE use the following general criteria for grading.

0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

***Attribution***

*Attribution* is defined as the determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories are as follows:

- *Unrelated* The adverse event is *doubtfully or clearly NOT related* to therapy
- *Related* The adverse event *is possibly, probably, or definitely related* to therapy

***Suspected Adverse Reaction***

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

***Unexpected Adverse Event***

An *unexpected adverse event* is any adverse event for which the specificity or severity is not listed in the package insert or the specificity or severity of which is not consistent with the package insert.

11.3 Routine Reporting

Grade ≥3 adverse events other than hematologic toxicities will be recorded, graded, and reported as appropriate. AEs will be collected from the time the patient signs consent until 30 days after discontinuation of all study treatment, or until the patient receives an alternative anti-cancer therapy, whichever date comes first. AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol. Myelosuppression and associated complications are expected events during leukemia therapy; therefore, myelosuppression and associated simple complications such as fever, infections, bleeding, lab abnormalities, and related hospitalizations will not be reported as individual AE but will be summarized in the annual report to the IRB as needed.

11.4 Expedited Reporting

In accordance with FHCC/UW Cancer Consortium IRB policy, all adverse events (AEs; whether occurring on-site or off-site), which in the opinion of the principal investigator (PI) are (1) unexpected, and (2) related or possibly related to the research, and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized, will be submitted to the IRB within ten (10) calendar days of learning of the problem. Both the "Expedited Reporting Form for Unanticipated Problems or Noncompliance" and the "Adverse Event Reporting Form", or equivalent forms, will be completed for this reporting.

11.5 Data Safety and Monitoring Plan

The Principal Investigator will carry out ongoing trial oversight and will meet frequently with the study team to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. All investigators on the protocol have received formal training in the ethical conduct of human research. The Principal Investigator will receive monitoring support as described below. Institutional support of trial monitoring will be in accordance with the FHCC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals

determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP. In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCC Scientific Review Committee (SRC) and the FHCC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study. The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

### 11.6 Required Records and Materials

Under the supervision of the investigators, research staff will maintain case report forms and secured databases on the relevant clinical and laboratory data. Records maintained in investigators' offices will be secured with access limited to study personnel. Authorization for access to medical records will be obtained from all patients in accordance with provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Original signed informed consent forms will be kept within the secured study team office, access is limited to study personnel. A copy of the signed informed consent form is given to the participant. Data will be collected on patient characteristics, disease characteristics, protocol therapy, response to treatment, adverse events and follow-up for relapse and survival. Copies of the patient's medical record including history and physical exams, documentation of protocol therapy, labs, scans, x-rays, hospitalizations, operative reports, pathology reports etc. are required.

## 12.0 ELEMENTS OF INFORMED CONSENT

All Institutional, NCI, State and Federal regulations concerning informed consent and peer judgment will be fulfilled. Written consent will be obtained from all patients entering the study.

## 13.0 REFERENCES:

1. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000;18:547-61.

2. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood 1995;85:2025-37.
3. Linker C, Damon L, Ries C, et al. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. J Clin Oncol 2002;20:2464-71.
4. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 2005;106:3760-7.
5. Stock W, Luger SM, Advani A, et al. Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia (ALL): Early Results of U.S. Intergroup Trial C10403. ASH Annual Meeting 2014;124: Abstract 796.
6. Gokbuget N. How I treat older patients with ALL. Blood 2013;122:1366-75.
7. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol 2012;13:403-11.
8. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-17.
9. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16:57-66.
10. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002;99:2685-93.
11. Lai GM, Chen YN, Mickley LA, et al. P-glycoprotein expression and schedule dependence of adriamycin cytotoxicity in human colon carcinoma cell lines. Int J Cancer 1991;49:696-703.
12. Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med 2013;369:1915-25.
13. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood 2014;124:2354-61.
14. Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood 2014;123:843-50.
15. Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood 2010;116:2070-7.
16. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175-81.
17. Ravandi F, Jorgensen JL, Thomas DA, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood 2013;122:1214-21.
18. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol 2015;16:1547-55.
19. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 2014;371:1005-15.

20. Maury S, Chevret S, Thomas X, et al. Addition of Rituximab Improves the Outcome of Adult Patients with CD20-Positive, Ph-Negative, B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL): Results of the Randomized Graall-R 2005 Study. ASH Annual Meeting 2015;126: Abstract 1.
21. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol 2010;28:3880-9.
22. Bruggemann M, Raff T, Kneba M. Has MRD monitoring superseded other prognostic factors in adult ALL? Blood 2012;120:4470-81.
23. Wu D, Sherwood A, Fromm JR, et al. High-throughput sequencing detects minimal residual disease in acute T lymphoblastic leukemia. Sci Transl Med 2012;4:134ra63.
24. Wu D, Emerson RO, Sherwood A, et al. Detection of minimal residual disease in B lymphoblastic leukemia by high-throughput sequencing of IGH. Clin Cancer Res 2014;20:4540-8.
25. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360:470-80.
26. Vitanza NA, Zaky W, Blum R, et al. Ikaros deletions in BCR-ABL-negative childhood acute lymphoblastic leukemia are associated with a distinct gene expression signature but do not result in intrinsic chemoresistance. Pediatr Blood Cancer 2014;61:1779-85.
27. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.
28. Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. Leukemia 2010;24:521-35.
29. Acute Lymphoblastic Leukemia (Version 2.2019). Available at: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf.
30. Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2011;118:6521-8.
31. Rousselot P, Coude MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood 2016;128:774-82.
32. Cassaday RD, Stevenson PA, Wood BL, et al. Description and prognostic significance of the kinetics of minimal residual disease status in adults with acute lymphoblastic leukemia treated with HyperCVAD. Am J Hematol 2018;93:546-52.
33. Cassaday RD, Alan Potts D, Jr., Stevenson PA, et al. Evaluation of allogeneic transplantation in first or later minimal residual disease - negative remission following adult-inspired therapy for acute lymphoblastic leukemia. Leuk Lymphoma 2016;57:2109-18.