International phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones

EsPhALL2017/COGAALL1631

EsPhALL network I-BFM Study Group **Children's Oncology Group**

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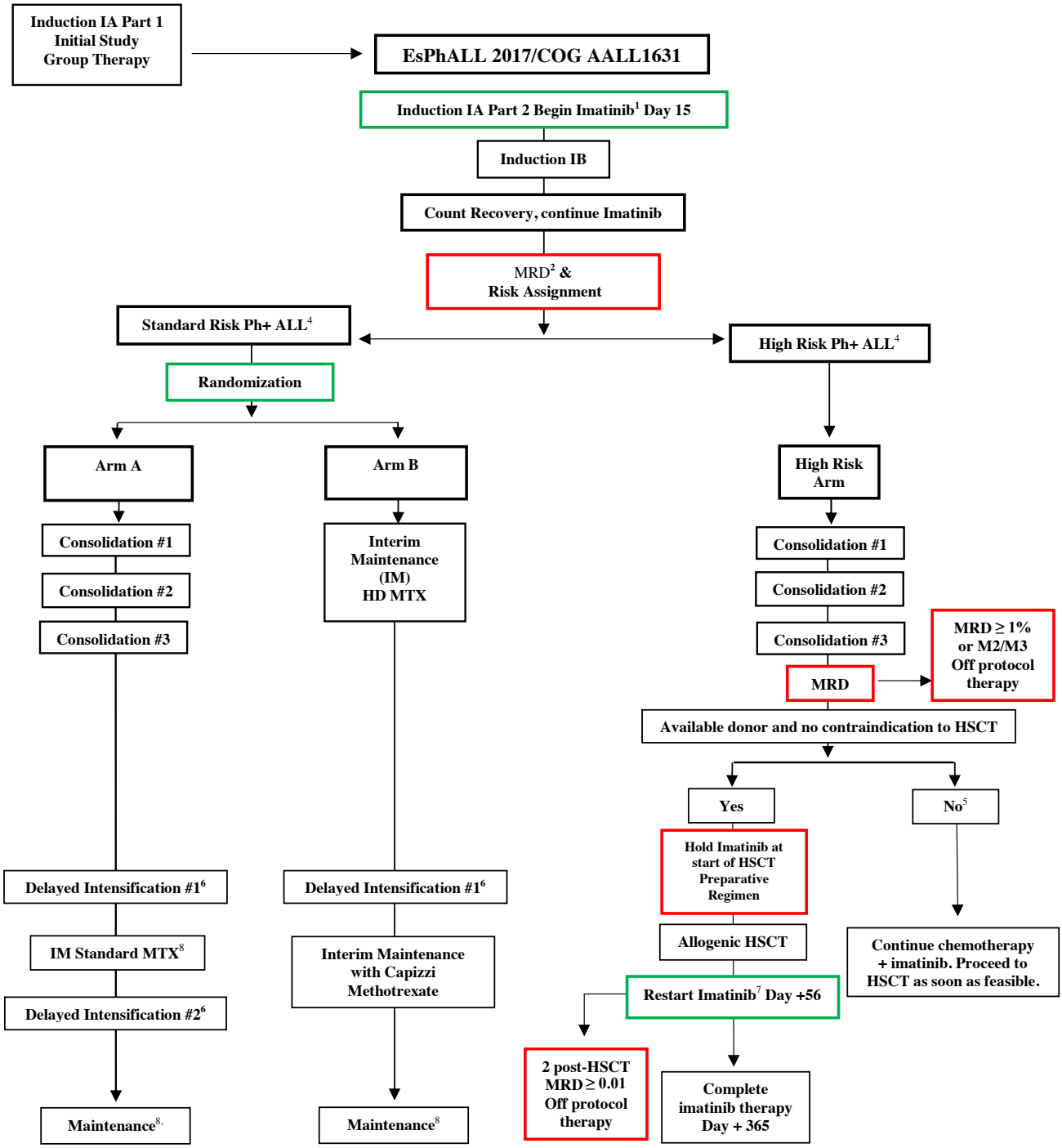
ABSTRACT

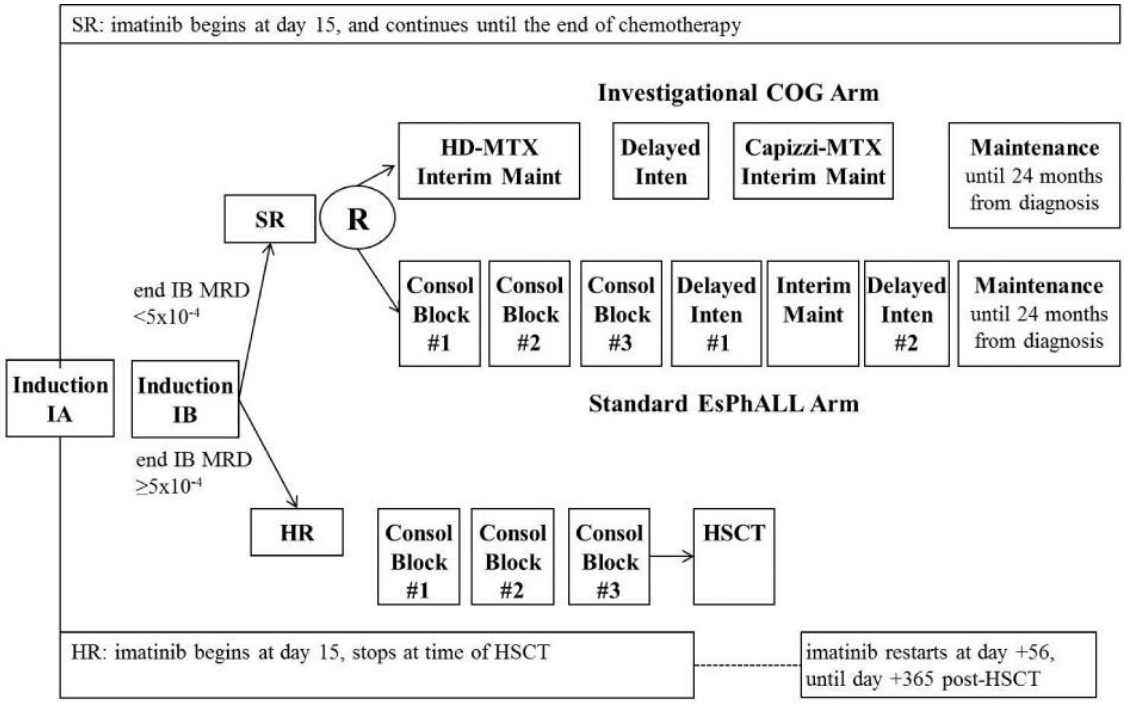
Approximately 3-5% of pediatric ALL patients present with the Philadelphia chromosome (Ph+ ALL). Historically, patients with Ph+ ALL had a poor prognosis and were considered candidates for allogeneic hematopoietic stem cell transplant (HSCT) in first complete remission (CR1). Studies conducted by COG and the European EsPhALL consortium over the last decade have demonstrated that the majority of pediatric Ph+ ALL patients are effectively treated with the combination of a tyrosine kinase inhibitor (TKI) and chemotherapy, without HSCT in CR1. However, the cytotoxic chemotherapy backbone administered in these trials was more intensive than is standardly used in COG for non-Ph+ pediatric B-ALL, resulting in high rates of treatment-related toxicities (including life-threatening infections) and mortality, as well as increased risk of late effects. Reduction in treatment-related toxicities, if achievable without compromising disease-free survival (DFS), would represent an important advance for this patient population. EsPhALL 2017/COG AALL1631 is an international collaborative protocol conducted by COG and EsPhALL with the primary objective of reducing treatment-related morbidity and mortality without adversely impacting DFS in Ph+ ALL patients classified as Standard Risk (SR) based on low minimal residual disease (MRD) at week 10-12 of therapy. Ph+ ALL patients will enter the trial at Day 15 of Induction IA and begin daily imatinib at that time. After the Induction IB phase (week 10-12), MRD will be assessed by immunoglubulin-T-cell-receptor (IgH-TCR) PCR, and patients will be classified as SR (those with MRD $< 5 \times 10^{-4}$) or High Risk (HR; MRD $\geq 5 \times 10^{-4}$). SR patients will be randomized to receive one of two cytotoxic chemotherapy backbones: 1) the EsPhALL backbone (Arm A) used in previous EsPhALL protocols and COG AALL1122/CA180372 or 2) a less intensive regimen similar to those typically administered to non-Ph+ ALL HR patients on COG trials (Arm B). Patients on both arms will continue to receive imatinib until the completion of all planned chemotherapy (two years of treatment). For HR patients (approximately 15-20% of patients), allogeneic HSCT in CR1 is still considered the treatment of choice. On EsPhALL 2017/COG AALL1631, HR patients will receive the EsPhALL chemotherapy backbone and proceed to HSCT after completion of the three consolidation blocks. Because there is variability in clinical practice regarding the use of TKI's post-HSCT in Ph+ ALL, and controversy regarding their impact on toxicity, graft-versus-host disease (GVHD) and Event Free Survival (EFS), we will test the feasibility and describe the outcome of post-HSCT imatinib administration in HR pediatric Ph+ ALL patients. Imatinib will be administered to all HR patients from Day +56 until Day +365 post-HSCT. This single-arm, Phase 3 study will be the largest prospective trial of a pediatric population uniformly treated with imatinib pre- and post-HSCT. At COG sites, adherence to imatinib, 6-mercaptopurine and methotrexate will be assessed in SR patients and to post-HSCT imatinib in HR patients in order to determine the prevalence, predictors and prognostic relevance of non-adherence in this patient population.

EXPERIMENTAL DESIGN SCHEMA



[1]Administer imatinib continuously throughout protocol unless otherwise noted. [2]MRD performed after count recovery from Induction IB.
[3]M1 defined in Section 3.3. [4] Refer to Section 4.1 for details on risk stratification
[5]Patients continue to receive the standard EsPhALL chemotherapy with imatinib. [6] Note: Delayed Intensification is 2-part.
[7]Resume Imatinib 56 days after allogenic HSCT when peripheral blood counts are met; continue through Day +365.
[8]Standard Risk patients with CNS3 leukemia at diagnosis receive cranial irradiation.
HDMTX: High Dose Methotrexate IM: Interim Maintenance MRD: Minimal Residual Disease HSCT: Hematopoietic Stem Cell Transplant

TREATMENT OUTLINE



Note. MRD: Minimal Residual Disease, SR:Standard Risk, HR: High Risk, **R**: Randomization, HD-MTX: High Dose Methotrexate, Maint: Maintenance, Inten: Intensification, Consol: Consolidation, HSCT: Hematopoietic Stem Cell Transplant

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1To compare disease-free survival (DFS) of Standard Risk (SR) pediatric Ph+ ALL treated with continuous imatinib combined with either a high-risk COG ALL chemotherapy backbone or the more intensive EsPhALL chemotherapy backbone.

1.2 Secondary Aims

1.2.1To determine the feasibility of administration of imatinib after allogeneic HSCT in High Risk (HR) Ph+ ALL patients.

1.2.2 To determine event-free-survival (EFS) of HR pediatric Ph+ ALL patients treated with EsPhALL chemotherapy, HSCT in first complete remission and post-HSCT imatinib.

1.2.3 To compare rates of Grade 3 or higher infections in SR Ph+ ALL patients between the two randomized arms.

1.2.4 To evaluate EFS and overall survival (OS) of all enrolled participants.

1.2.5 To evaluate OS in SR patients.

1.2.6 To evaluate OS in HR patients.

1.3 Exploratory Aims

1.3.1 To describe the toxicities associated with post-HSCT administration of imatinib.

1.3.2 To evaluate the long-term toxicities in SR patients treated with chemotherapy plus imatinib (no transplant), overall and between randomized arms.

1.3.3 To determine prognostic significance of MRD in Ph+ ALL at various time points during therapy.

1.3.3.1 To determine the prognostic significance of MRD at end of Induction IA.

1.3.3.3 To evaluate MRD in HR patients just prior to HSCT and then at regular intervals post-HSCT and explore the association of these measurements with long-term outcome.

1.3.3.4 To evaluate concordance of MRD assessments made by IGH-TCR PCR assay and Next Generation Sequencing (NGS) assays.

1.3.4 To determine prognostic significance of *IKZF1* gene aberrations and deletions.

1.3.5 To determine frequency and prognostic significance of p190 and p210-*BCR-ABL1* fusion variants in pediatric Ph+ ALL.

1.3.6 To measure adherence to oral chemotherapeutic agents (imatinib, 6-mercaptopurine and methotrexate) for 6 months during the maintenance phase in SR Ph+ ALL patients in COG Centers only.

1.3.6.1 To identify factors associated with poor adherence.

1.3.6.2 To determine association between relapse risk and adherence to each oral chemotherapeutic agent (separately and combined).

1.3.7 To measure adherence to imatinib after allogeneic HSCT in HR Ph+ ALL patients and identify factors associated with poor adherence for COG centers only.

2.0 BACKGROUND

2.1 Introduction

2.1.1 General Overview

The optimal treatment for children and adolescents with Ph+ ALL has not yet been determined. There is now a general consensus among the North American and European Childhood ALL treatment groups that Ph+ ALL patients with a favorable early response to the combination of chemotherapy and tyrosine kinase inhibitor (TKI) treatment can be treated without HSCT in first complete remission (CR1), while those with a suboptimal early response are more appropriately treated with HSCT in CR1. Two different cytotoxic chemotherapy backbones have been used in combination with TKI in recent North American and European pediatric Ph+ ALL trials: 1) the COG regimen (used in COG AALL0031 with imatinib and in AALL0622 with dasatinib), and 2) the EsPhALL regimen used in Europe and other Countries with imatinib (EsPhALL trial) and in a joint COG/EsPhALL (AALL1122/ CA180372) trial with dasatinib. Both of these regimens are quite intensive, leading to a high frequency of treatment-related complications, including prolonged myelosuppression and life-threatening infections. On AALL1122/CA180372, approximately 5% of patients treated with the EsPhALL regimen plus TKI without HSCT died due to toxicity, accounting for a significant percentage of events observed in the non-HSCT population in these trials. The goal of this trial is to reduce treatment-related morbidity and mortality without adversely impacting DFS in SR patients, who comprise approximately 80-85% of all pediatric Ph+ ALL patients. The proposed EsPhALL2017/COGAALL1631 trial will test whether favorable outcomes may be achieved when imatinib is combined with a less intensive chemotherapy backbone in pediatric Ph+ ALL patients defined as SR based on MRD measurements early in treatment. We plan to randomly compare the two cytotoxic backbones using a non-inferiority design in order to detect whether there is a lack of significant decrement in DFS with the less intensive chemotherapy regimen. The randomized trial design will also allow us to directly compare toxicities associated with the two regimens.

2.2 Rationale for Selected Approach and Trial Design

2.2.1 International Collaboration

Because pediatric Ph+ ALL is uncommon, randomized Phase 3 trials in this population are only feasible if conducted as an international collaboration. The recently completed AALL1122/CA180372 trial demonstrated the ability of

COG and the multinational European EsPhALL group to successfully cooperate and efficiently conduct a large, international trial. EsPhALL 2017/COG AALL1631 trial is a joint effort by COG and EsPhALL.

2.2.2 Less Intensive Cytotoxic Chemotherapy Combined with Imatinib in SR Ph+ ALL Patients

Recent studies conducted by COG and the European EsPhALL Consortium have demonstrated that the combination of a TKI with a cytotoxic chemotherapy backbone results in a relatively favorable event free survival (EFS). However, these trials have utilized a cytotoxic chemotherapy backbone that is more intensive than is standardly used in COG or non-Ph+ pediatric B-ALL, resulting in high rates of treatment-related toxicities (including life-threatening infections), protracted myelosuppression and more frequent and longer hospitalizations. Treatment-related mortality on these regimens is much higher than is observed with more standard ALL regimens, and accounts for a significant proportion of the events observed on these trials. Additionally, these regimens include agents not typically administered during CR1 in other ALL patients (such as ifosfamide and etoposide), and higher cumulative dosages of other agents (such as cyclophosphamide and anthracyclines), which may increase risk of late effects. Reduction in treatment-related toxicities, if achievable without compromising DFS, would represent an important advance for this patient population.

It is not clear how much the intensity of the cytotoxic chemotherapy backbone contributes to the reduction in relapse risk in TKI-treated Ph+ ALL patients, and the more frequent occurrence of treatment-related mortality with more intensive regimens creates a competing risk. By predisposing to serious treatment complications, more intense cytotoxic regimens may cause disruptions and/or reductions in TKI dosing, which potentially could increase relapse risk. Intensive chemotherapy backbones may also limit the ability to dose escalate TKI and/or add other agents that might potentiate their benefits in future trials. Additionally, the intense cytotoxic regimens make it more challenging to bring these treatments to areas of the world where maximal supportive care is not readily available.

We hypothesize that, for patients with a favorable early response to chemotherapy and TKI, treatment with a less intensive chemotherapy regimen (ie, one more standardly used for non-Ph+ B-ALL in COG trials) will result in reduced treatment-related toxicity without a significant decrement in DFS.

Ph+ ALL patients will enter the trial at Day 15 of Induction IA and begin daily dosing of imatinib at that time. They will complete the remainder of the Induction IA phase, have a bone marrow performed to assess response, and then proceed to Induction IB. A bone marrow will be performed at the time of count recovery to assess MRD. Patients with low End-IB MRD ($< 5 \times 10^{-4}$) will be classified as SR and those with high End-IB MRD ($\geq 5 \times 10^{-4}$) will be classified as HR. SR patients will continue imatinib and receive one of two chemotherapy regimens: 1) Arm A (based on the EsPhALL/COG AALL1122/CA180372 protocols) or 2) Arm B (based on COG AALL0232 for non-Ph+ HR ALL). Arm B represents a significant reduction in intensity of cytotoxic chemotherapy. The

cumulative dosage of anthracycline and alkylating agents will be significantly lower on the arm B, and patients treated on this arm will not receive high-dose cytarabine, ifosfamide or etoposide, all of which are components on the EsPhALL arm (Arm A).

We will compare DFS between arms, as well as the frequency of acute toxicities (including Grade 3 or higher infections) and late effects (including echocardiographic abnormalities and incidence of second malignant neoplasms). Ultimately, if successful, the proposed trial would establish a new, less toxic standard-of-care that would be more feasible to administer to children world-wide. It would also pave the way for intensification of TKI therapy and/or use of additional or alternative targeted agents in future trials.

Total Cumulative Doses of Chemotherapy by Treatment Arm (EsPhALL2017/COGAALL1631)[*]

	Arm A (EsPhALL)	**Arm B (Investigational COG)**
Anthracycline (daunorubicin, doxorubicin)	280 mg/m^2	125 mg/m^2
Cyclophosphamide	5 gr/m^2	3 gr/m^2
Ifosfamide	4 gr/m^2	None
Etoposide	500 mg/m^2	None
High-dose Cytarabine	12 gr/m^2	None
High-dose Methotrexate (5 gr/m^2)	2 doses	4 doses
Escalated-dose Methotrexate (100 mg/m^2)[**]	None	5 doses
Dexamethasone	580 mg/m^2	140 mg/m^2
Prednisone/Prednisolone	840 mg/m^2	4040 mg/m^2
Vincristine	14 doses	30 doses
Pegaspargase (2500 IU/m^2)	5 doses	4 doses
Intrathecal chemotherapy	18 doses	17 doses

[*] Not including chemotherapy administered on Days 1-14 of Induction IA, prior to study enrollment
[**] Starting dose

2.2.3 Feasibility of Post-HSCT TKI in HR Ph+ ALL

Whether TKIs should be administered after HSCT to Ph+ ALL patients is an unresolved issue, especially in the pediatric population. There are conflicting data from studies of adults with Ph+ ALL treated with prophylactic post-HSCT TKI, and very little published pediatric data. The toxicity of post-HSCT TKI, and its impact on GVHD and relapse risk, has not been defined in the pediatric Ph+ ALL population. Thus, its use has typically been left to the discretion of the treating clinician, without data-driven guidelines. EsPhALL-COG 2017 study of post-

HSCT TKI in HR Ph+ ALL patients will provide much needed data to help guide clinical care of this patient population.

After Induction IB phase, HR patients on EsPhALL 2017/COG AALL1631 will continue chemotherapy per the EsPhALL chemotherapy backbone, with the plan that they will proceed to allogeneic HSCT after recovery from the third Consolidation block. We will evaluate the feasibility of post-HSCT imatinib administration in HR patients. HR patients will begin imatinib at Day +56 post-HSCT (or at the time of engraftment, whichever comes later) to avoid any overlapping end-organ toxicity related to preparative regimen. Starting at this time point is also likely to avoid any overlap with the onset of acute GVHD. On COG protocol ASCT0431 (a randomized study of sirolimus added in post-transplant setting in ALL patients), patients who experienced Grades 1-3 acute GVHD by Day +55 had a lower risk of relapse (presumably as a result of a graft-versus-leukemia effect), but the development of chronic GVHD was not associated with relapse risk.[1] Of note, 93% of patients who developed acute GVHD on that trial did so by Day +55. Imatinib and other TKIs have been used to treat chronic GVHD.[2] Thus, starting imatinib at Day +56 should avoid any interference in the development of acute GVHD, which could potentially have a beneficial anti-leukemic effect, but might prevent or ameliorate chronic GVHD. COG Centers will assess the proportion of patients who receive at least 75% of intended doses, while both COG and EsPhALL Centers will prospectively collect data on targeted toxicities, including neutropenia, thrombocytopenia, abnormalities of liver function tests and infection.

2.2.4 Minimal Residual Disease (MRD) Testing by Immunoglobulin (Ig)/T-cell Receptor (TCR) Clonality

Minimal Residual Disease (MRD) will be the only factor used to risk-stratify Ph+ ALL patients enrolled on EsPhALL 2017-COG AALL1631. All patients will have MRD assessed (via marrow sample) after recovery from the Induction IB phase of therapy (week 10-12). Patients with low MRD at this timepoint (defined as $< 5 \times 10^{-4}$) will be classified as SR and will be eligible for randomized comparison of two treatment arms (EsPhALL arm (Arm A) vs Investigational (Arm B)). Those with high MRD (defined as $\geq 5 \times 10^{-4}$) will be classified as HR, and will be allocated to allogeneic HSCT after completion of three blocks of consolidation chemotherapy. Data from the AIEOP-BFM group indicate that non-Ph+ B-ALL patients with high end-IB MRD who have persistently high MRD after the 3 intensiveonsolidation blocks have an extremely poor prognosis, even if they go onto receive allogeneic HSCT. Thus, HR patients on EsPhALL 2017/COG AALL1631 will have MRD tested at the end-consolidation Block 3 timepoint and will be removed from study treatment if MRD is persistently high ($\geq 10^{-2}$) at that time point.

Several methodologies are available to assess MRD in ALL, including quantitative polymerase chain reaction (RQ-PCR) of rearranged immunoglobulin (Ig)/T-cell receptor (TCR) genes (IgH/TCR PCR), RQ-PCR of fusion transcripts (such as *BCR-ABL1*) and flow cytometry. The IgH/TCR PCR test has been the primary test used in AEIOP-BFM trials and several other European clinical trial

groups. On AALL1122/CA180372, MRD in Ph+ ALL patients was assessed by the IgH/TCR PCR assay, with flow cytometry and RQ-PCR of BCR-ABL1 fusion transcripts serving as back-up tests. Allocation to HSCT was made based on end-IB MRD, using the same cut-off as EsPhALL2017/COGAALL1631. There was very high concordance in MRD results between the assays, with very few patients (<1%) having discordant results that would have resulted in a different transplant recommendation. 84% of patients had evaluable IgH/TCR PCR results. Flow cytometry was the more reliable back-up test; of the patients in whom MRD could not be determined by the IgH/TCR PCR assay, all had evaluable flow MRD results. Based on this experience, MRD on EsPhALL2017/COGAALL1631 will be assessed primarily by IgH/TCR PCR, with flow cytometry as back-up; *BCR-ABL1* PCR results will not be used for clinical decision-making.

2.2.5 Choice of Tyrosine Kinase Inhibitor (TKI)

Previous trials of TKI-based therapy in pediatric Ph+ ALL have utilized either continuous dosing of imatinib (AALL0031, amended EsPhALL) or dasatinib (AALL0622, AALL1122/CA180372). The overall EFS rates appear similar amongst these trials. Additionally, the proportion of patients on AALL1122/CA180372 (dasatinib + chemotherapy) with end-IB MRD < 5×10^{-4} (80-85%) was nearly identical to that of the amended EsPhALL trial, which treated patients with the same chemotherapy backbone, but used imatinib instead of dasatinib. Thus, the available data from previous trials does not indicate that there is any clear benefit of one TKI over the other, either in terms of early response or long-term outcome. Because it is more readily available in all participating countries, imatinib was chosen as TKI to be combined with chemotherapy on EsPhALL2017/COGAALL1631.

2.3 Relevant Data

2.3.1 Chemotherapy and TKI in Pediatric Ph+ ALL

Approximately 3-5% of pediatric ALL patients present with the Philadelphia chromosome [t(9;22)(q34;q11.2)]. Historically, Ph+ ALL was associated with a poor prognosis, with long-term EFS rates of ~30%. In a retrospective analysis of 610 pediatric Ph+ ALL patients treated in the pre-TKI era (1995-2005), by 10 study groups, the 7-year EFS was 32% and overall survival (OS) was 44.9%.[3] Compared with chemotherapy alone, HSCT in CR1 was associated with a superior EFS after adjusting for waiting time to transplantation (44% vs 34%, p=0.049). This study also demonstrated that a favorable early response (measured by either peripheral blood response to steroid prophase or early marrow morphologic response to multiagent chemo) was a significant and independent predictor of superior long-term outcome.

COG AALL0031 (2002-2006) tested the combination of imatinib (beginning after the 4-week remission Induction phase) and an intensive chemotherapy backbone. On that trial, Ph+ and non-Ph+ very high risk (VHR) patients received the same cytotoxic regimen (including cyclophosphamide to a cumulative dose of 11 gm/m^2, 9 gm/m^2 ifosfamide, 3.5 gm/m^2 etoposide and 9 courses of high-dose MTX). There was no difference in the frequency of most Grade 3 or higher

toxicities for Ph+ patients (who received imatinib) and non-Ph+ patients (who did not). Infection with Grade 3/4 neutropenia, transaminitis and hypokalemia were observed more often in Ph+ ALL patients compared with other VHR patients who did not receive imatinib.[4]

On AALL0031, patients with an HLA-matched sibling were allocated to HSCT in CR1; the intent was for all other patients to complete the VHR chemotherapy backbone along with imatinib, although some patients without an HLA-matched sibling were taken to unrelated donor HSCT. The 3-year EFS rate for all 44 Ph+ ALL patients who received continuous dosing of imatinib (340 mg/m^2/day, Cohort 5), including transplanted and non-transplanted patients, was 80 $\pm$ 11%, markedly better than historic controls treated without TKI (EFS 35 $\pm$ 4%).[4] These favorable results have been maintained with longer follow-up.[5] Importantly, there was no DFS advantage demonstrated with HSCT, although patient numbers were small. The 5-year DFS for non-transplanted patients in Cohort 5 treated with chemotherapy plus imatinib was 71±12% (n=28), not significantly different than the DFS of patients treated from all cohorts with HSCT: 5-year DFS of 64±12% for related donor HSCT patients (n=21) and 63±16% for unrelated donor HSCT patients (n=13) (p=0.77).[5]

The successor COG study AALL0622 (2008-2012) evaluated the feasibility of administering dasatinib on a chemotherapy backbone similar to that of AALL0031. On AALL0622, dasatinib was started on Day 15 of Induction (rather than after completion of Induction as on AALL0031), which resulted in improved Induction CR rates compared to the previous AALL0031 trial, as well as increased frequency of low MRD levels at early time points in therapy,[6] thus indicating that earlier introduction of TKI (mid-induction) was both feasible and favorably impacted early response. Patients were risk classified on the basis of MRD; patients with levels $\geq$ 1% at end-Induction and/or $\geq$ 0.01% at end-Consolidation were considered HR; all others were classified as SR. Allogeneic HSCT was recommended for all HR patients and for any SR patient with a matched sibling donor. The combination of dasatinib with chemotherapy was well tolerated, without excessive toxicity noted. The overall 3-year EFS was 79±6% (n=58 evaluable patients), similar to the 3-year EFS observed on the AALL0031 (imatinib) trial. SR patients, 19% of whom underwent HSCT, exhibited a 3-year EFS of 83±6% and HR subjects, 78% of whom underwent SCT, had a 3-year EFS of 63±19%.[7] Follow-up on this study is ongoing and the EFS estimates are not yet stable with several events occurring after 3 years. While not a randomized comparison, there is no clear suggestion that outcome on AALL0622 (dasatinib) was superior to AALL0031 (imatinib). Data regarding post-HSCT TKI use was not prospectively collected on AALL0622.

While these two COG trials were being conducted, several European clinical trials groups joined together to form the multinational EsPhALL Consortium to test the combination of TKI and a different chemotherapy backbone in pediatric Ph + ALL. The chemotherapy regimen used in the EsPhALL trials was based on that used for the highest risk non-Ph+ ALL patients on trials conducted by the AIEOP-BFM groups. This high-risk backbone included three post-Induction Consolidation blocks (“HR blocks”), two Delayed Intensification phases, and

cranial radiation for all patients.[6,8] The intensified phase of treatment on the EsPhALL regimen was shorter than that on AALL0031 and AALL0622, and total cumulative doses of alkylating agents and epipodophyllotoxins were significantly lower.

The initial EsPhALL trial (2004-2009) tested in a randomized fashion the use of imatinib in Good Risk (GR) patients (defined by peripheral blood response to prednisone prophase, early marrow morphologic response during the Induction phase and morphologic response at the end of Induction); Poor Risk (PR) patients were non-randomly assigned to receive imatinib. Imatinib on that trial was discontinuously dosed beginning after the Induction phase, and HSCT was recommended for patients with either a matched related or unrelated donor. When analyzed by intent-to-treat, imatinib was associated with a trend toward better 4-year DFS in GR patients (73% vs 62%, p=0.24); the as-treated analysis showed a 4-year DFS of 75% for GR patients receiving imatinib and 56% for those who did not (p=0.06).[8] However, because imatinib exposure on the EsPhALL trial was much less than on the COG trial, and approximately 70% of patients on the EsPhALL trial received an allogeneic HSCT in CR1, results of the EsPhALL trial were not able to confirm the promising results of the initial COG trials that TKI + chemotherapy may replace HSCT.

The EsPhALL trial was amended in 2010 to test continuously dosed imatinib on the same chemotherapy backbone, with fewer patients being allocated to HSCT in CR1; enrollment to the amended trial closed in December 2014. 154 patients were enrolled on the amended trial, 104 (67%) assigned to GR group and 50 (33%) classified as PR. With a median follow-up of 34 months, the 3-year EFS of GR patients was 68%, similar to the outcome of GR patients in the initial EsPhALL trial; however, far fewer GR patients on the amended EsPhALL trial received an allogeneic HSCT in CR1 than on the initial EsPhALL trial (31% vs 77%). Thus, it appears that the use of continuous imatinib effectively replaced allogeneic SCT in the majority of GR patients treated on the EsPhALL chemotherapy backbone. The 3-year EFS of patients on the amended EsPhALL trial who had low MRD ($< 5 \times 10^{-4}$) at the end of the IB phase was ~70%.

An international collaborative COG/EsPhALL trial (AALL1122/CA180372) opened in 2012 with the objective of determining the EFS of pediatric Ph+ ALL patients treated with continuously-dosed dasatinib (starting at day 15 of the Induction phase) combined with the EsPhALL chemotherapy backbone. The AALL1122/CA180372 trial was conducted at 93 COG sites in the US and Canada, and 29 EsPhALL sites in the United Kingdom and Italy. The trial met its accrual goal of 105 patients in two years and closed to enrollment in May 2014. As noted above, the proportion of patients on AALL1122/CA180372 (who met the MRD definition of Good Risk, (ie, end IB MRD $< 5 \times 10^{-4}$), was nearly identical to that of the amended EsPhALL trial, which treated patients with the same chemotherapy backbone, but used imatinib instead of dasatinib. Estimates of long-term DFS and OS for patients treated on AALL1122 awaits longer follow-up.

Toxic deaths, almost all due to infection, have occurred among patients treated with chemotherapy plus TKI on both the EsPhALL trial and the COG/EsPhALL (AALL1122/CA180372) trial. The toxic death rate appears to be about 5%, is not obviously different on the imatinib and dasatinib trials, and these deaths account for a significant proportion of events observed among SR/GR patients. These deaths occurred primarily during the intensive Consolidation cycles. Thus, it is possible that a less intensive chemotherapy backbone may reduce non-relapse deaths, and even improve EFS, among SR Ph+ ALL patients.

2.3.2 Post-transplant TKI in HR Ph+ ALL

There is wide variation in practice regarding the use of TKIs after allogeneic HSCT for Ph+ ALL, with only a few published studies providing data regarding the toxicity and efficacy of this approach. The largest study suggesting that post-HSCT TKI may be beneficial came from European Group for Blood and Marrow Transplantation (EBMT) who published a retrospective analysis of 473 adult patients who received an allogeneic HSCT in CR1 for Ph+ ALL, 60 of whom had received TKI (primarily imatinib) as post-HSCT prophylaxis.[9] TKI was initiated a median of 83 days after HSCT; duration was not specified. The overall 5-year DFS for the whole population was 38% and OS 46%. Multivariate analysis indicated that prophylactic post-HSCT TKI was associated with more favorable DFS (Hazard Ratio [HR] 0.44, p=0.002) and OS (HR 0.42, p=0.004). Post-HSCT TKI was also associated with a lower cumulative incidence of acute GVHD (HR 0.57, p=0.02). Data regarding toxicity of post-HSCT imatinib was not available in this retrospective series.

Some smaller studies, again primarily including mostly adult patients, suggest that TKI administration post-HSCT is not associated with excessive toxicity. In a series of 22 patients with high risk Ph+ leukemia (15 with Ph+ ALL and 7 with CML) imatinib was administered post-HSCT beginning at the time of engraftment; the most common adverse events were grades 1-3 nausea, emesis and transaminitis.[10] However, there were only 3 pediatric patients enrolled on that study, and it appeared that they tolerated a lower dose of imatinib than adults. In another study from China, prophylactic post-HSCT imatinib was administered to 62 patients (including 10 pediatric patients) with Ph+ ALL at a starting dose of 400 mg/day in adults in 260 mg/m^2/day in children.[11]. Imatinib was initiated at a median of 70 days post-HSCT. Grade 3-4 AEs occurred in 11 (18%) of patients, and were predominantly related to myelosuppression, nausea/vomiting and edema. All were reversible. Ten patients (16%) stopped imatinib within 90 days of initiation of treatment due to toxicity. Toxicity rates by age group were not reported.

There are very few reports of pediatric Ph+ ALL patients treated with post-HSCT TKI. On COG AALL0031, 21 patients underwent a matched sibling HSCT, including 8 of 39 in cohorts 1-4 (discontinuous dosing of imatinib pre-HSCT) and 13 of 44 in cohort 5 (continuous pre-HSCT imatinib at 340 mg/m^2/day).[4] All 21 patients received post-HSCT imatinib beginning 4-6 months after transplant for a total of 6 months. Post-HSCT imatinib was started at 230 mg/m^2/day and escalated to 340 mg/m^2/day if no Grade 3 or 4 toxicities occurred within the first

28 days. Total duration of post-HSCT imatinib treatment was 6 months. There were no significant post-HSCT toxicities noted in these 21 patients, and their 3-year EFS was 56.6 ± 21.5%. However, no data were collected on the actual doses of imatinib received.

Other COG Ph+ ALL protocols have not included specific recommendations regarding post-HSCT TKI. On AALL0622 and AALL1122/CA180372, the use of dasatinib post-HSCT was optional (left to discretion of treating clinician) and post-HSCT toxicity related to TKI was not prospectively collected.

The results of AALL0031 provide pilot data suggesting that post-HSCT imatinib appears feasible in pediatric Ph+ ALL patients. However, there are several issues that limit the interpretability of the findings: 1) small patient numbers, especially the number of patients receiving continuous dosing of imatinib pre-HSCT (n=11); 2) the relatively late start day of imatinib (day 120-180); 3) the initial low starting dose of imatinib for the first 28 days of treatment; and 4) duration of post-HSCT therapy of only 6 months.

EsPhALL2017/COGAALL1631 will build upon the pilot AALL0031 data regarding post-HSCT imatinib but with several key differences: 1) larger patient cohort (with a uniform pre-HSCT imatinib exposure); 2) earlier start date post-HSCT; 3) longer duration of imatinib post-HSCT; 4) improved capture of target toxicities and imatinib dose received post-HSCT.

2.4 Correlative Studies

2.4.1 Prognostic Factors in Pediatric Ph+ ALL

There are very few identified prognostic factors in pediatric Ph+ ALL patients treated with TKI. This trial, which will enroll over 600 patients, will be the largest trial ever conducted in pediatric Ph+ ALL, and so provides us the unique opportunity to identify novel prognostic factors that may help to refine risk stratification (and allocation to HSCT) in future studies. We will evaluate the prognostic significance of a number of biologic factors, including *IKZF1* gene deletions, *BCR-ABL1* fusion variants (p190 versus p210), and *BCR-ABL1* kinase domain mutations associated with TKI resistance. We will also assess MRD at multiple time points during therapy. Recent studies in non-Ph+ ALL have indicated that poor adherence to oral 6-mercaptopurine is associated with increased relapse risk; therefore, COG Centers will also assess the frequency and prognostic impact of non-adherence to imatinib (and other oral chemotherapeutic agents), and identify predictors for non-adherence that may be amenable to intervention in the future. This study will be the first to systematically evaluate TKI adherence in pediatric Ph+ ALL.

2.4.2 Prognostic Significance of Minimal Residual Disease (MRD)

2.4.2.1 MRD at the End of Induction IA

Multiple studies have demonstrated that end-induction MRD is an important, independent predictor of outcome in non-Ph+ pediatric B-ALL.[12,13] End-induction MRD is used by almost all clinical trials groups as a factor

determining the intensity of post-induction treatment, with patients found to have higher levels allocated to more intensive therapies.

Early response to therapy, as assessed by peripheral blood response to prednisone prophase or early marrow morphologic response to multi-agent induction has also been shown to be an important predictor of outcome in Ph+ ALL in the pre-TKI era.[3] However, data regarding the prognostic significance of end-induction MRD levels are more limited in the post-TKI era due to small patient numbers. On EsPhALL-COG 2017, patients will be risk-stratified based on end-IB MRD, as was done on the previous Ph+ ALL trial, AALL1122/CA180372. On the AIEOP-BFM 2000 trial, patients with both Ph+ and non Ph+B ALL with high end-IB MRD had the highest risk of treatment failure (overall hazard ratio 7.51, $p< 0.001$).[14] Marrow samples will be collected at the end of Induction IA in all Ph+ ALL patients enrolled on EsPhALL-COG 2017 for MRD assessment, but the results will not be used for clinical decision-making or treatment allocation.

2.4.2.2 MRD in High Risk Patients Pre- and Post-Hematopoietic Stem Cell Transplant (HSCT)

Results from AIEOP-BFM studies indicate that non-Ph+ ALL patients with high end-IB MRD who have persistent MRD after receiving the three Consolidation blocks (identical to those administered on the EsPhALL arm (Arm A) of EsPhALL 2017/COG AALL1631) have an extremely high risk of relapse (personal communication, Martin Schrappe, MD). We will assess MRD levels at the end of third Consolidation Block in all HR patients. Patients with MRD $\geq 10^{-2}$ at this time point will be removed from protocol therapy and be considered candidates for alternative therapies. We will explore the prognostic significance of lower levels of MRD at this time point.

Several studies have demonstrated that the level of MRD at the time of HSCT is a key risk factor in children with ALL undergoing allogeneic HSCT, with significantly higher risk of relapse in patients who are MRD-positive pre-HSCT compared with those who are MRD non-detectable.[15-17] We will explore the prognostic impact of pre-HSCT MRD in the context of post-HSCT TKI therapy. It is anticipated that most HR patients will proceed to HSCT immediately after Consolidation Block 3; thus, the sample collected at that time point will serve as the pre-HSCT assessment. For HR patients whose transplants occur at later time points during therapy, we will obtain an additional sample for MRD assessment just prior to starting the preparative regimen for HSCT.

The presence of detectable MRD post-HSCT has been also associated with an increased risk of subsequent relapse in childhood ALL.[15,17,18] Given this risk, many centers now standardly monitor post-HSCT MRD in patients and intervene (e.g., by rapidly weaning immunosuppression) in patients found to have high levels. We will assess MRD at the start of post-HSCT MRD (Day +56), and then again at Day +90, Day +180 and at the completion of post-HSCT imatinib (Day +365). We will describe the proportion of patients who become MRD positive over time, as well as explore the impact of post-HSCT imatinib in reducing MRD in patients with detectable MRD at the first time point (Day +56). Given the high risk of relapse associated with high levels of

post-HSCT MRD, any HR patient found to have MRD $\geq 10^{-2}$ on two consecutive post-HSCT measurements will be removed from protocol therapy so that alternative treatments can be pursued (e.g., rapid withdrawal of immune suppression or change to alternative TKI).

2.4.2.3 Concordance of MRD Assessments made by IgH-TCR PCR assay and Next Generation Sequencing (NGS) assay

In approximately 15-20% of samples tested by the IgH-TCR PCR assay are "indeterminate", primarily due to failure to identify an IgH/TCR clone or develop a PCR probe of sufficient sensitivity for MRD detection. An alternative Next Generation Sequencing (NGS) approach for MRD detection has been developed and validated.[19,20] The NGS methodology utilizes high-throughput sequencing to identify clonal rearrangements of IgH and TCR genes in diagnostic samples and to quantify MRD in follow-up samples. There are several potential advantages to NGS MRD assays, including greater sensitivity (able to detect much lower levels of disease than flow cytometry), a lower rate of indeterminate results than IgH/TCR MRD assays, and the ability to assess MRD in multiple subclones with distinctive IgH and/or TCR rearrangements.

In a study conducted by St. Jude Children's Research Hospital (SJCRH), NGS methodology was compared with multiparameter flow cytometry and IgH-TCR PCR assays using diagnostic and follow-up samples from 106 patients with ALL. The NGS assay detected MRD in all 28 samples shown to be positive by flow cytometry and in 35 of the 36 shown to be positive by IgH-TCR PCR, and detected MRD in 10 and 3 additional samples that were negative by flow cytometry and Allele-Specific Oligonucleotide (ASO)-PCR, respectively.[19] In a retrospective study conducted by the DFCI ALL Consortium, MRD could be successfully quantitated by the NGS assay in 37 end-Induction samples for which the IgH-TCR MRD assay had yielded indeterminate results; MRD level as assessed by NGS MRD was strongly associated with outcome.[21]

To test whether the increased sensitivity of NGS MRD assessments better identifies pre- and post-HSCT relapse risk compared with flow cytometric MRD techniques, COG investigators compared the two methodologies using banked samples from 56 B-ALL patients treated on ASCT0431.[15] At the pre-transplant time-point, NGS MRD predicted relapse and survival more accurately than flow cytometry-MRD ($P < .0001$). None of the patients identified as pre-HSCT MRD-negative by NGS subsequently relapsed compared with 16% of those who had been considered MRD-negative by the less sensitive flow cytometric assay. Post-HCT, the NGS assay was also better at predicting relapse than flow cytometry ($P < .0001$). These data suggest that the NGS assay is better able to identify very low levels of MRD that are prognostically important but are missed by flow cytometric techniques.

On EsPhALL2017/COGAALL1631, we plan to prospectively evaluate NGS MRD in HR patients and compare results obtained with this assay and those from IgH-TCR PCR and flow cytometry. We will explore concordance of MRD assessments made by NGS PCR and other assays (IgH-TCR PCR, flow cytometry) and whether the the greater sensitivity of the NGS MRD assay helps to identify a high risk group of patients missed by the other tests, at the end-IB time point as well as in the peri-transplant period for HR patients.

2.4.3 Prognostic Significance of *IKZF1* Gene Aberrations and Deletions

Alterations of the *IKZF1* gene are present in a large proportion of childhood and adult Ph+ ALL and in cases of blast-crisis chronic myelogenous leukemia (CML). [22] In one study, *IKZF1* deletions have also been identified in ~15% of patients without BCR-ABL rearrangements.[23] In the BCR-ABL negative cases, *IKZF1* deletions have been shown to have independent prognostic significance, carrying a three-fold increase risk of treatment failure.[23]

There are limited data regarding the prognostic significance of *IKZF1* gene aberrations in pediatric Ph+ ALL. In a retrospective study of 191 patients treated between 1995 through 2010, with available diagnostic samples, *IKZF1* deletions (found in 66% of the tested cohort) were associated with significantly worse disease-free and overall survival rates.[24] However, in a subset analysis including only patients treated on the initial EsPhALL trial (most of whom received imatinib), the trend toward inferior outcome with *IKZF1* deletions did not achieve statistical significance. The interpretation of these results is limited because: 1) the patient number was small, limiting the power to detect clinically meaningful differences in outcome 2) imatinib was administered only intermittently on the EsPhALL trial, and 3) the majority of patients went to HSCT in CR1.

EsPhALL2017/COGAALL1631 will be the first prospective evaluation of *IKZF1* status in a large cohort of uniformly –treated Ph+ ALL patients treated with continuous imatinib. This analysis will focus on full gene coding region of *IKZF1* (exons 2-8). A targeted *IKZF1* copy number microarray will be used to detect *IKZF1* deletions in specimens from diagnosis. Thus, we will be able to evaluate the prognostic significance of different *IKZF1* deletion and copy number variants, which was not possible on the previous retrospective pediatric study because of the small number of available samples.

2.4.4 Prognostic Significance of *BCR-ABL1* Fusion Variants in Pediatric Ph+ ALL

The t(9;22) results in the *BCR-ABL1* fusion gene, leading to dysregulation of transcriptional control and constitutive activation of a tyrosine kinase with multiple downstream targets important for cellular proliferation, evasion of apoptosis, and genomic instability. Two different forms of *BCR/ABL1* are observed in Ph+ ALL: p190 and p210. The p190 form is the most common variant observed in de novo Ph+ ALL, and is only rarely observed in chronic myeloid leukemia (CML). p210 is the predominant form of *BCR/ABL1* found in hematopoietic cells of patients with CML in stable phase, although it has been observed in some cases of Ph+ ALL. Some cases of p210 Ph+ ALL may represent CML presenting in lymphoid blast crisis, although the exact proportion is unknown.

In adult Ph+ ALL, approximately 50% of patients have a p210 form of *BCR/ABL1*. The proportion appears to be much lower in pediatric Ph+ ALL: 10-15% of pediatric Ph+ ALL patients have the p210 breakpoint. The prognostic significance of the p210 transcript has not been previously evaluated in pediatric Ph+ ALL, and there are only limited available data from adult Ph+ ALL studies. Cimino and colleagues (2006) reported the results from the GIMEMA 0496

protocol of 101 adult Ph+ ALL patients, 60% of whom had a p190 transcript and 40% had a p210.[25] Presence of p210 was associated with a significantly worse outcome; on multivariable analysis, presence of the p190 fusion transcript was the only independent favorable prognostic factor (HR: 0.52, p=0.021). These data suggest that *BCR-ABL1* fusion variant may be an important predictor in Ph+ ALL; however, none of the patients on the GIMEMA trial received TKI and overall outcomes were worse than are typically observed in pediatric Ph+ALL patients with current regimens. We will determine the *BCR-ABL1* fusion isoform for all patients enrolled on EsPhALL2017/COGAALL1631 to determine whether fusion type is a significant prognostic factor in the context of a TKI-based regimen. Additionally, determination of BCR-breakpoint may identify a small number of patients with p210 fusion who, with further testing and history-taking, are found to actually have CML in lymphoid blast crisis rather than de novo ALL and therefore would be considered ineligible for EsPhALL2017/COGAALL1631.

2.4.5 Prognostic Significance of Non-adherence to Oral Chemotherapy in Pediatric ALL

Recently published studies conducted by COG investigators indicate that poor adherence to oral 6-mercaptopuine (6-MP) in children and adolescents with ALL is an important predictor of relapse.[26-28] Using objective methods to monitor adherence (MEMS Caps) have yielded a critical level of non-adherence associated with an increased risk of relapse. These studies have demonstrated that the prevalence of non-adherence (adherence rate <95%) is 44% among children with ALL, and that 47% of the relapses observed among children entering remission in 1st CR are attributable to non-adherence. The cumulative incidence of relapse was significantly greater (17.0% ± 3.7%) among patients with adherence rate <95% when compared with patients with higher adherence rates (4.9% ± 1.9%; p=0.001). Factors associated with higher risk of non-adherence included older age (≥ 12 years), non-white race/ethnicity, low annual household income/ low parental education, household structure (single mother/ multiple children) and absence of a routine surrounding pill taking.[26-28]

Pediatric Ph+ ALL patients treated with oral imatinib represent an especially vulnerable population because of the presumed importance of daily TKI administration for successful treatment. Previous studies indicate an association between complex therapeutic regimens and non-adherence. However, adherence to TKI and other oral chemotherapy agents has not been previously been systematically evaluated in this population. Furthermore, adherence to oral imatinib after HCT (and with the need for additional medications surrounding HCT) has not been examined. COG Centers plan to address this gap in the current trial for patients enrolled at COG institutions. Other groups from EsPhALL network might be interested to this study too.

2.4.5.1 Medication Event Monitoring System (MEMS ®)

The MEMS® *TrackCap*™ (MEMS: Westrock Switzerland Ltd, Switzerland) is a child-resistant cap that fits standard medication vials and contains a microelectronic chip that records each time the container is opened, providing a means to measure adherence. The data is stored in the

MEMS memory for up to 3 years. Patients are instructed not to open the container unless taking a dose of the medication and to remove only the prescribed dose each time the container is opened. The patients return their MEMS® *TrackCap*™ to the clinic at the end of the study; data is downloaded via the MEMS® MAP modem, yielding a record of times and dates that the pill container was opened during the study period. They facilitate the collection of real-time patient adherence data and allow the investigator to understand and analyze the patients' medication-taking patterns so that this information can be correlated with clinical parameters.[29-31] Opening the container does not guarantee that pills are taken out or swallowed. However, this approach provides the most accurate and valuable data in adherence research and has advanced our knowledge of medication-taking behavior.[32]

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration and Study Screening

3.1.1.1 Patient Registration in Relevant National Database

Prior to enrollment in this study, patients must be assigned a patient ID number within the national front-line ALL protocol (Group patient Number, GPN). Each group in the EsPhALL network is required to follow the relevant national SOPs for patients' registration.

3.1.1.2 Study Screening and Registration in Study Database

Subsequently, and promptly after BCR/ABL1 fusion detection, patients must be screened for assessment of eligibility criteria (see Section 3.2) and registered into the web-EsPhALL study database, available at www.web-esphall.trialcenter-unimib.org. Each participating site is required to complete the Screening and Registration forms in the web-EsPhALL database. Screening data as per Section 3.2 must be reported for all patients, including those not enrolled in the study, in order to monitor any selection bias. The following schema summarizes necessary steps to be taken during the pre-enrollment phase.

Protocol day	Actions
d0	New diagnosis of ALL
d0-d1	• start of national front-line ALL treatment • registration into national database as per national SOPs • GPN assignment
d0-d14	BCR/ABL1 detection
d8-d15	• EsPhALL2017/COGAALL1631 study screening • study site enters the Screening/Registration and Eligibility forms into web-EsPhALL database
d10-d15	Patient is eligible / Patient is not eligible **EsPhALL2017/COGAALL1631 enrollment** / other protocol / other protocol
d15	**start of therapy**

Flow chart of steps prior to study enrollment. GPN = group patient number (according to national ALL database)

3.1.2 IRB/CE Approval

This protocol will be opened to accrual at sites indicated by the national groups, after study approval by Ethics Committees and regulatory authorities as appropriate according to national laws.

3.1.3 Study Enrollment

Prior to patient enrollment, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form.

Patient enrollment must be promptly communicated to the National Trial Unit for documentation in the study database.

3.1.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.5 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

3.1.6 Randomization

Via the trial database, randomization for SR Ph+ ALL patients will take place at the end of Induction IB, when MRD has been determined. The treatment will be randomly assigned based on the statistical design of the trial.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are >7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC

with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

3.2.1 Availability of Diagnostic Bone Marrow Samples

Patients should be enrolled on the National ALL front-line protocol prior to enrollment on EsPhALL2017/COGAALL1631, so that diagnostic samples have been collected and analyzed according to the procedures of the National ALL front-line protocol.
For patients who were not previously enrolled on the National ALL front-line protocol, baseline diagnostic samples must be available to develop an MRD probe.

3.2.2 Age

> 1 year and ≤ 21 years at ALL diagnosis

3.2.3 Diagnosis

3.2.3.1Newly diagnosed de novo ALL (B-ALL or T-ALL) with definitive evidence of *BCR-ABL1* fusion by karyotype, FISH and/or RT-PCR

Regardless of initial front-line protocol diagnostic samples laboratory reports detailing evidence of *BCR-ABL1* fusion must be available for the National Trial Unit.

3.2.4 Prior Therapy

Please see Section 4.1 for the concomitant therapy restrictions for patients during treatment.

3.2.4.1 Patient must have previously started Induction therapy, which includes vincristine, a corticosteroid, usually PEG-L-Asparaginase, with or without anthracycline, and/or other standard cytotoxic chemotherapy.

3.2.4.2 Patient has not received more than 14 days of multiagent Induction therapy beginning with the first dose of vincristine.

3.2.4.3 Patient may have started imatinib prior to study entry but has not received more than 14 days of imatinib.

3.2.5 Performance Status

Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. (Please refer to the performance status scale in Appendix VIII)

3.2.6 Organ Function Requirements

3.2.6.1 Adequate liver function defined as:

Direct bilirubin ≤ 2.0 mg/dL.

3.2.6.2 Adequate cardiac function defined as:

- Shortening fraction of ≥27% by echocardiogram, or
- Ejection fraction of ≥50% by radionuclide angiogram or echocardiogram.
- Corrected QT Interval, QTc < 480mSec

Note: Repeat echocardiogram is not required if echocardiogram was obtained within 21 days of study enrollment.

3.2.6.3 Adequate renal function is defined as:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m2 , or
- Serum creatinine within normal limits based on age/gender, as follows:

Age	Maximum Serum creatinine (mg/dL)	
	Male	Female
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

3.2.7 Exclusion Criteria

3.2.7.1 Known history of chronic myelogenous leukemia (CML).

3.2.7.2 ALL developing after a previous cancer treated with cytotoxic chemotherapy.

3.2.7.3 Active, uncontrolled infection or active systemic illness that requires ongoing vasopressor support or mechanical ventilation

3.2.7.4 Down syndrome

3.2.7.5 Pregnancy and Breast Feeding

a. Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
b. Lactating females who plan to breastfeed their infants.
c. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

3.2.7.6 Patients with congenital long QT syndrome, history of ventricular arrhythmias or heart block.

3.2.7.7 Prior treatment with dasatinib, or any *BCR-ABL1* inhibitor other than imatinib.

3.2.8 Regulatory Requirements

All patients and/or their parents or legal guardians must sign a written informed consent.

3.3 Definitions

INITIAL WBC (at the time of ALL diagnosis): The first WBC at the treating institution, or the WBC prior to intravenous fluids, whichever occurred first. If prior therapy (i.e. steroids) has been administered and a CBC is available that was obtained within 72 hrs prior to steroid therapy, then this pre-steroid WBC should be used.

CNS LEUKEMIA:

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 of < 5/μL WBCs and cytospin positive for blasts; or traumatic lumbar puncture (LP), ≥ 5/μL WBCs, cytospin positive for blasts, 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 (see below).

CNS3: In CSF, non-traumatic LP presence of ≥ 5/μL WBCs and cytospin positive for blasts, or traumatic LP, ≥ 5/μL WBCs, cytospin positive for blasts, and positive by Steinherz/Bleyer algorithm, 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 (see below);
CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain involvement or hypothalamic syndrome).

METHOD OF EVALUATING 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 to distinguished between CNS2 and CNS3 disease:

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

A patient with CSF WBC ≥ 5/μL 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 = 3.0 X 10^6/μL:

$$\frac{60}{1500} = 0.04 > 2X \frac{46000}{3.0 \times 10^6} = 0.015$$

TESTICULAR LEUKEMIA AT DIAGNOSIS: Unilateral or bilateral testiculomegaly consistent with leukemic infiltration.

BONE MARROW STATUS:
M1: < 5% lymphoblasts
M2: 5%- 24% lymphoblasts
M3: ≥ 25% lymphoblasts

RESISTANT DISEASE
MRD ≥ 10^{-2} assessed by IgH-TCR-PCR (or ≥1% if assessed by flow cytometry) or morphologic residual disease (M2 marrow confirmed by flow cytometry or *BCR-ABL1* FISH; or M3 marrow) at the end of Consolidation Block 3.

RELAPSE
Any recurrence of disease whether in marrow or extramedullary site. Relapse should be confirmed by examination of sample from involved site (marrow, spinal fluid, testicle, etc.).

1) ISOLATED BONE MARROW RELAPSE: Patients with an M2 (5-24% blasts by morphology with confirmatory testing consisting of ≥ 5% lymphoblasts by flow cytometry or *BCR-ABL1* FISH or ≥10^{-2} leukemic clone identified by IgH-TCR PCR) or M3 marrow (≥ 25% blasts by morphology; confirmatory testing is not required) at any point after achieving remission without involvement of the CNS and/or testicles.

2) CNS RELAPSE: Positive cytomorphology and WBC ≥ 5/µL or clinical signs of CNS leukemia such as facial nerve palsy, brain involvement, or hypothalamic syndrome. If any CSF evaluation shows positive cytomorphology and WBC < 5/µL, a second CSF evaluation is required within 2-4 weeks. While identification of a leukemic clone in CSF by flow cytometry (TdT, CD19, CD10, etc) or FISH for diagnostic karyotypic abnormality may be useful, definitive evidence of CNS involvement (i.e. WBC ≥ 5/µL OR clinical signs of CNS leukemia) is required for the diagnosis of a CNS relapse.

3) TESTICULAR RELAPSE: Must be documented by testicular biopsy, if not associated with a marrow relapse.

4) ISOLATED EXTRAMEDULLARY RELAPSE: Relapse occurring in CNS or testicle, as defined above, or other extramedullary site (e.g., eye, lymphomatous mass) documented by biopsy. without concurrent M2 or M3 marrow involvement.

5) COMBINED RELAPSE:
   A. COMBINED MARROW/EXTRAMEDULLARY RELAPSE: M2 or M3 marrow at any point after achieving remission with concomitant CNS and/or testicular and/or other sites relapse.
   B. COMBINED EXTRAMEDULLARY RELAPSE: Two or more extramedullary sites of relapse without morphologic marrow involvement (i.e. M1 marrow)

6) PROGRESSIVE DISEASE AFTER HSCT: MRD ≥ 10^{-2} (assessed by IgH-TCR-PCR (or ≥1% if assessed by flow cytometry) at two post-HSCT time points separated by at least 2 weeks, or relapse (as defined above) at any post-HSCT time point.

4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. 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 where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

All patients will begin Induction IA according to the institutional standard of care.

Patients will begin imatinib once daily at the time of trial enrollment, or earlier but no more than two weeks before enrollment. Section 4.2 describes the treatment. Induction IA will last approximately 29 to 33 days depending on the institutional standard of care.

Informed consent describing the first 6 weeks of Induction therapy should have been previously obtained prior to study enrollment and is required for all patients. Initial informed consent for study will describe daily administration of imatinib and treatment through the end of Induction IB phase. There will be separate post-Induction IB consents depending on assigned risk group. The post-Induction IB consents for the SR Ph+-ALL patients includes randomized assignment to either EsPhALL backbone chemotherapy (arm A) with daily imatinib therapy, or the less intensive investigational chemotherapy backbone based on COG HR protocol (arm B).

After study entry, all patients should receive at least 14 days of imatinib along with the rest of Induction IA therapy. At the end of Induction IA, a bone marrow aspirate should be performed and patients will proceed to Induction IB phase regardless of morphologic response. Marrow MRD testing will be performed at the end of Induction IA but will not be used for risk group assignement or treatment allocation. Two weeks after the end of Induction IB, another bone marrow aspirate will be performed in the presence of count recovery; the recovery period may last up to 4 weeks. Imatinib alone will be administered until end Induction IB MRD results are available and the final risk group is assigned.

End Induction IB MRD results will be used to risk-stratify patients, as follows:

Standard risk (SR): MRD < 5×10^{-4}

High risk (HR): MRD ≥ 5×10^{-4}

MRD will be assessed as follows: by RQ-PCR of rearranged immunoglobulin/T-cell receptor genes (IgH/TCR). For patients with uninformative IgH/TCR rearrangements, MRD will be assessed by flow cytometry. . If flow cytometry is used to assess end-IB MRD, then the values defining SR will be < 0.05% and HR will be ≥ 0.05%. See Section 14.1 for

details. Note: *BCR-ABL1* fusion testing by PCR will not be used for MRD determination.4.1.1 Imatinib Administration

Imatinib 340 mg/m^2 once daily (up to a maximum of 800 mg/dose) will be introduced at the time of study entry and will be given continuously until the end of therapy (2 years from the start of Induction IA). Imatinib should only be interrupted for toxicity (See Section 5.7). The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, the dose may be rounded to the nearest 50 mg dose.

After end-Induction IB marrow is performed, imatinib alone may be administered for up to 4-weeks to allow time for MRD testing for risk stratification.

4.1.2 Standard Risk (SR) Ph+ ALL

Imatinib alone will be administered for up to four weeks to allow time for MRD testing for risk stratification. After risk group assignment, SR Ph+ ALL patients will be randomized to 1 of 2 regimens:

Arm A (EsPhALL Arm): Current EsPhALL chemotherapy backbone + imatinib

Arm B (Investigational COG Arm): COG HR chemotherapy backbone + imatinib

SR Ph+ ALL patients who decline randomization will come off protocol therapy after completion of the IB phase and will be considered inevaluable for randomized comparisons of DFS and toxicity; however, they will be included in reports of OS/EFS for all enrolled subjects.

Phases of Therapy for Arm A (EsPhALL Arm):
Post Induction therapy includes 3 Consolidation blocks, 2 Delayed Intensification phases, 1 Interim Maintenance phase with standard-dose oral methotrexate (EsPhALL IM), and Maintenance therapy that continues until 24 months from the start of Induction IA. See the experimental design schema.

Phases of Therapy for Arm B (Investigational COG Arm):
Post Induction therapy includes an Interim Maintenance phase with high dose methotrexate (IM with High Dose MTX), a Delayed Intensification phase, a second Interim Maintenance phase with Capizzi (escalating dose) Methotrexate (IM with Capizzi), and Maintenance therapy that continues until 24 months from the start of Induction IA. See the experimental design schema.

Cranial Radiation Therapy:
Patients with CNS3 status at diagnosis receive cranial irradiation, 1800 cGy in 10 fractions, during Interim Maintenance in the Arm A (EsPhALL Arm), and during Maintenance therapy (in the first 4 weeks) in the Arm B (Investigational COG Arm).

4.1.3 High Risk (HR) Ph+ ALL

HR Ph+ ALL patients will be directly assigned to HR treatment arm (standard EsPhALL backbone), and allocated to HSCT in CR1. HSCT should occur as soon as feasible after recovery from Consolidation Block #3. A bone marrow aspirate should be performed after recovery from Consolidation Block #3. Patients with high MRD ($\geq 10^{-2}$) will be considered to be off-protocol therapy. The only subsequent data collected from these patients will be whether or not they undergo HSCT and the date of HSCT, the time of relapse or second event (if applicable), and survival status (alive/dead) every 6 months. These patients will be included in disease free survival (DFS) and overall survival reports, but will not be considered in evaluating the toxicity of the regimen (after the time of study departure), or the feasibility of administering imatinib post-HSCT.

Once patients proceed to HSCT, the donor, preparative regimen, and GVHD prophylaxis is at discretion of the treating clinician/national group standards. Post-HSCT imatinib is to be started at Day +56 or at the time of ANC/platelet engraftment (whichever occurs later).

Patients should continue to receive the chemotherapy per the EsPhALL backbone arm with imatinib until the time of HSCT if they are not ready to undergo HSCT upon recovery from Consolidation Block #3. If alternative non-protocol chemotherapy is given (including a TKI other than imatinib), patients will be considered to be off protocol therapy at that time. The only subsequent data collected from these patients will be whether or not they undergo HSCT and the date of HSCT, the time at which a first event occurs (if applicable), and survival status (alive/dead) every 6 months. These patients will be included in DFS and overall survival reports, but will not be considered in evaluating the toxicity of the regimen (after the time of study departure), or the feasibility of administering imatinib post-HSCT.

HSCT should occur within 6 months from the start of Delayed Intensification #1 phase; if HSCT has not occurred by that time (some HR Ph+ ALL patients will not have a suitable HSCT donor identified, or will not be fit enough to undergo HSCT), then HR Ph+ ALL patients should continue therapy on the EsPhALL chemotherapy backbone with imatinib until 24 months from the start of Induction IA and will only be considered off protocol therapy if they meet the criteria discussed above. HR patients who do not proceed to HSCT and who were CNS-3 at diagnosis should receive cranial radiation during Interim Maintenance phase (See Section 4.23.3). All other HR patients who do not proceed to HSCT will be treated without cranial radiation and they will receive intrathecal methotrexate during maintenance as in EsPhALL Arm.

Phases of Therapy for the HR (EsPhALL) Arm:
Post Induction therapy includes 3 Consolidation blocks, with HSCT after recovery from Consolidation Block #3. Patients who do not proceed to HSCT will receive 2 Delayed Intensification phases, 1 Interim Maintenance phase with EsPhALL Interim Maintenance, and Maintenance therapy that continues until 24 months from the start of Induction IA. See the experimental design schema.

4.1.4 Concomitant Therapy Restrictions

4.1.4.1 Drug Interactions with Imatinib

The use of concomitant moderate-strong CYP 3A4 inducers or inhibitors should be avoided whenever possible in patients receiving imatinib. Please refer to Appendix II for a list of CYP 3A4 inducers and inhibitors.

4.1.4.2 Cytochrome P450 Interactions with Antileukemic Drugs

Since concurrent use of enzyme inducing anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazepine) with antileukemic therapy has been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes. Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsant. Azole antifungals (listed in the table below) and the macrolide group of antibiotics (listed in the table below) may have potent inhibitory effects on drug-metabolizing enzymes. Patients receiving some antileukemic drugs (e.g., vincristine, anthracyclines, etoposide) may experience excess toxicity when these agents are given concomitantly; alternate antifungal and antibacterial therapy should be used where possible (see table below).

DRUGS	POTENTIAL INTERACTION	ACTION TO BE TAKEN
Anticonvulsants	Induction of drug metabolizing enzymes Lowered EFS	AVOID phenytoin, phenobarbital, carbamazepine Consider gabapentin or levetiracetam as alternative
Rifampin	Induction of drug metabolizing enzymes	DO NOT USE
Azole Antifungals (fluconazole, itraconazole*, posaconazole voriconazole, ketoconazole)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine*, anthracyclines, etoposide, steroids
Macrolide Antibiotics (erythromycin, clarithromycin, azithromycin, roxithromycin, telithromycin)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine, anthracyclines, etoposide, steroids

* Itraconazole should NOT be used in patients who are receiving vincristine due to a serious drug-drug interaction leading to severe neurotoxicity.[33,34]

For a more complete list of CYP3A4/5 Inhibitors and Inducers, see Appendix II

4.1.4.3 Possible Drug Interactions with High or Intermediate Dose Methotrexate

Avoid non-steroidal anti-inflammatory drugs (NSAIDs) trimethoprim/sulfamethoxazole (TMP/SMX), penicillins, probenecid, IV contrast media, proton pump inhibitors, phenytoin, and fosphenytoin. Urinary acidifiers can cause methotrexate to precipitate in the urinary tract.

For supportive therapy each group follows its own guidelines.

4.2 Induction IA Part 2

4.2.1 Therapy Delivery Map – Induction IA Part 2 Induction IA Part 2 is 2 weeks, Days 15-33: days calculated from the administration of the first dose of vincristine. Note: if native L-Asp product was started in Induction IA Part 1 the course planned should be completed during Induction IA Part 2.	_____ Patient number _____ DOB

Treatment details and criteria to start are in Section 4.2.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.2.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Predniso(lo)one (PRED)	PO	60 mg/ m^2/day	15-28	Total daily dose: 60 mg/ m^2, divided BID. Refer to Section 4.2.3 for admin guidelines.
Vincristine (VCR)	IV over 1 min	1.5 mg/ m^2/dose **Maximum dose: 2 mg**	15 & 22	Or infusion via minibag as per institutional policy.
Daunorubicin* (DAUN)	IV over 1-15 mins	25 mg/ m^2/dose	15 & 22	May be infused over the course of 1 hour. Refer to Section 4.2.3 for admin guidelines. *Should **not** be given to patients who began Induction IA on or as per DFCI Consortium protocol.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8mg 2-2.99 10mg ≥3 12mg	29 #**CNS3 also on 15 & 22**	Refer to Section 4.2.3 for admin guidelines. **Note age-based dosing.**

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	PRED ____mg	VCR ____mg	DAUN ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below					
		15	____mg	____mg ____mg	____mg	____mg	____mg #	a-c, f-m
		16		____mg ____mg				
		17		____mg ____mg				
		18		____mg ____mg				
		19		____mg ____mg				
		20		____mg ____mg				
		21		____mg ____mg				
		22		____mg ____mg	____mg	____mg	____mg #	a-c
		23		____mg ____mg				
		24		____mg ____mg				
		25		____mg ____mg				
		26		____mg ____mg				
		27		____mg ____mg				
		28		____mg ____mg				
		29					____mg	a-f
		33	M1 marrow, begin Induction IB when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3 x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Continue daily imatinib until Induction IB begins. M2 or M3 marrow at the end of Induction IA, proceed to Induction IB immediately, irrespective of hematologic values.					

See **Section 5.0** for Dose Modifications for Toxicities

4.2.2 Required Observations in Induction IA Part 2

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bone marrow evaluation. For patients who consent, submit a bone marrow sample for MRD testing. Please refer to Section 14.2
e. CSF cell count and cytospin
f. Bilirubin, ALT, and creatinine
g. Pregnancy test, if applicable
h. Bone age
i. ECG (Can be collected prior to or during Days 1-15 of Induction IA)
j. MUGA or ECHO (Can be collected prior to or during Days 1-15 of Induction IA)
k. Performance status
l. TPMT and NUDT15 genotype (optional)
m. For patients who did not enroll on national frontline protocol, submit reports of Ph+ status to the National Trial Unit for central review.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.2.3 Treatment Details for Induction IA Part 2

All patients will receive Induction IA Days 1-14 according to the institutional standard of care.

Induction IA Part 2 is 2 weeks, Days 15-33: days calculated from the administration of the first dose of vincristine.

Note: if native L-Asp product was started in Induction IA Part 1 the course planned should be completed during Induction IA Part 2.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg**
- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily beginning on Day 15
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be continued without interruption until Induction IB begins.

See Appendix VI for details.

Predniso(lo)ne: Oral (may be given IV)

Days 15-28

Dose: 30 mg/m^2/dose BID; Total daily dose: 60 mg/m^2/day divided BID

Note: If a patient is unable to take prednisso(LO)ne by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Note: Patients who have receieved dexamethasone during Induction IA Part 1 (prior to study enrollment) should be switched to predniso(LO)ne for Induction IA Part 2 (after study entry).

Vincristine: Intravenous push or infusion via minibag per institutional policy

Days: 15 and 22

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

Note: Patients should receive no more than 4 total weekly doses of vinCRIStine during Induction IA. It is assumed that patients will have received 2 weekly doses of vinCRIStine (Days 1 and 8) during Induction IA part 1, prior to study entry, and therefore should receive Day 15 vincristine at start of Induction IA part 2 (at study entry). However, if a patient has already received a 3rd weekly dose of vinCRIStine prior to study entry, then Day 15 vincristine dose specified here, should be omitted.

Daunorubicin: Intravenous over 1-15 minutes
Day: 15 & 22
Dose: 25 mg/m^2/dose
Note: May be administered over 1 hour per institutional guidelines.

Note: Patients should receive no more than 4 total weekly doses of Daunorubicin during Induction IA. Day 15 Daunorubicin should be omitted in any patient who has already received 3 weekly doses of Daunorubicin prior to study entry.

Note: Patients who have already received 2 consecutive daily doses of Doxorubicin during Induction IA part 1 (e.g., as part of DFCI Consortium studies) should not receive daunorubicin on Days 15 and 22.

The reconstituted solution or the commercially available solution (5 mg/mL) can be administered (undiluted or diluted) by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that daunorubicin be administered through the tubing of a rapidly infusing solution of D_5W or 0.9% NaCl, infused into a large vein or central venous access device. Protect from sun light.

Special precautions: Medication errors have occurred due to confusion between daunorubicin and doxorubicin. daunorubicin is available in a liposomal formulation (DAUNOrubicin citrate, DaunXome®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intrathecal
Day: 29
Age-based dosing
Note: For HR B-ALL CNS3, also on Days 15 & 22

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥3	12 mg

Research Studies
Submit bone marrow sample for MRD testing. Refer to Section 14.2 for details.

See Section 5.0 for Dose Modifications based on Toxicities.

Continue to Induction IB therapy no sooner than day 33 of Induction IA or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, and direct bilirubin ≤ 3x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Patients with M2/M3 marrow at the end of Induction IA should proceed to Induction IB regardless of blood counts.

4.3 Induction IB

4.3.1Therapy Delivery Map – Induction IB Induction Therapy IB is for all patients. Begin Induction IB no sooner than 4 days from Induction IA. Induction IB is 6 weeks (42 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.3.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.3.3 for additional details. Imatinib is given daily without interruption Hold only for toxicity (Section 5.7)
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/ m^2/dose	1 & 28	
Mercaptopurine (MP)	PO	60 mg/ m^2/day	1-28	Refer to Section 4.3.3 for admin guidelines. .
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/ m^2/dose	3-6, 10-13, 17-20, & 24-27	Refer to Section 4.3.3 for admin guidelines. Must have **ANC ≥ 300/µL** and **platelets ≥ 30,000/uL** to start each 4-day Cytarabine block beginning on Days 10, 17, and 24
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1-1.99 / 8 mg 2-2.99 / 10 mg ≥ 3 / 12 mg	10& 24	**Note: Age based dosing**

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	CPM ____mg	MP ____mg	ARAC ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg	____mg	____mg		a-d
		2				____mg		
		3				____mg		
		4				____mg		
		5						
		6						
		8				____mg		c, e
		9				____mg		
		10				____mg		
		11				____mg		
		15				____mg		c, e
		16				____mg		
		17				____mg		
		18				____mg		
		22				____mg		c, e
		23				____mg		
		24				____mg		
		25				____mg		
		28		____mg				c-d
		42						f

Administer Imatinib alone until End IB- MRD results are available and final risk group/randomized arm is assigned (See Section 4.3.3). Begin the next course when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, and direct bilirubin ≤ 3x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). If the start of the next course of therapy is delayed for 2 weeks due to myelosuppression (i.e. if myelosuppression persists 2 weeks after ending Induction IB therapy), imatinib should be held, see Section 5.7.

See Section 5.0 for Dose Modifications for Toxicities

4.3.2 Required Observations in Induction IB

a.	Physical exam
b.	Height, weight
c.	CBC with diff/platelets
d.	Creatinine, AST/ALT, bilirubin
e.	CSF cell count and cytospin
f.	Bone marrow aspirate (**perform after recovery from Induction IB,**when ANC ≥ 500/µL and platelets ≥ 50,000/µL)
g.	Collect bone marrw for MRD assessment by PCR and flow cytometry. Note: *BCR-ABL1* fusion testing by PCR will not be used for MRD determination. Refer to Section 14.1 for sample and shipping details for PCR MRD testing.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.3.3 Treatment Details for Induction IB

For supportive therapy each group follows its own guidelines.

Begin Induction IB when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3 x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis no worse than Grade 1 (whichever occurs later).

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Orally
Days: Daily
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.
Note: Administer doses > 600 mg/ day divided twice daily

Imatinib should be given daily throughout phase, and while awaiting End Induction IB MRD results, risk classification and start of next treatment phase.

See Appendix VI for details.

Cyclophosphamide: Intravenous over 30-60 minutes
Days: 1 and 28
Dose: 1000 mg/ m^2/dose
Note: Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion

Mercaptopurine: Oral
Days: 1-28

Dose: 60 mg/m^2/day

Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 420 mg/m^2 (28-day cumulative dose is 1680 mg/m^2).
See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status.

Cytarabine: Intravenous over 1-30 minutes or Subcutaneous
Days: 3-6, 10-13, 17-20 & 24-27
Dose: 75 mg/m^2/dose

Note: Must have **ANC ≥ 300/µL** and **platelets ≥ 30,000/uL** to start each 4-day Cytarabine block beginning on Days 3, 10, 17, and 24 Days

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Methotrexate: Intrathecal
Days: 10 and 24
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥3	12 mg

Required Disease Evaluation
Bone marrow aspirate should be obtained at time of count recovery after completion of Induction IB. Count recovery defined as ANC ≥ 500/µL and platelets > 50,000/µL. Submit bone marrow sample for PCR and flow cytometry MRD testing. Refer to Section 14.1. Note: *BCR-ABL1* fusion testing by PCR will not be used for MRD determination.

See Section 5.0 for Dose Modifications based on Toxicities.

Patients in morphologic complete remission (M1 marrow) with end Induction IB **MRD < 5 x 10^{-4}**, are classified as **Standard Risk** and will be randomized to either **Arm A (EsPhALL Arm)** or Arm B (**Investigational COG Arm).**

- Standard Risk patients randomize to the **Arm A (EsPhALL Arm)**, begin the Consolidation Block #1 Section 4.4 when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, AST/ALT < 10x ULN, and direct bilirubin ≤ 3 x upper limit of normal (ULN), and mucositis no worse than Grade 1 (whichever occurs later).

- Standard Risk patients randomized to the Arm B (**Investigational COG Arm)**, begin Interim Maintenance with High Dose Methotrexate Section 4.14 when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, AST/ALT < 10x ULN, and direct bilirubin ≤ 3 x upper limit of normal (ULN), and mucositis no worse than Grade 1 (whichever occurs later).

Patients in morphologic remissionwith end Induction IB **MRD ≥ 5 x 10^{-4}**, and any patient with morphologically evident disease (M2 marrow confirmed by flow cytometry or *BCR-ABL1* FISH or M3 marrow) are classified as **High Risk** and are directly assigned to the **High Risk Arm**. Post-Induction IB therapy begins with Consolidation Block #1 Section 4.19 when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, AST/ALT < 10x ULN, direct bilirubin ≤ 3x upper limit of normal (ULN), and mucositis no worse than Grade 1 (whichever occurs later).

4.4 Consolidation Block #1 SR Ph+ALL Arm A (EsPhALL Arm)

4.4.1 Therapy Delivery Map – Consolidation Block #1 SR Ph+-ALL Arm A (EsPhALL Arm)

Begin Consolidation therapy after recovery from Induction IB, after risk group and randomized treatment arm assigned, when starting criteria are met. Consolidation Block #1 therapy is 3 weeks (21 days).

_____ Patient ID number

_____ DOB

Treatment details and criteria to start are in Section 4.4.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day,divided twice daily. See Section 4.4.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal MAH: Methotrexate (IT MTX) Cytarabine (ITARAC) Hydrocortisone (IT HC)	IT	Age (yrs) MTX ARAC HC 1-1.99 8 mg 20mg 8mg 2-2.99 10 mg 26mg 10mg ≥ 3 12 mg 30 mg 12mg	1	Administer ± 6 hours of the start of HDMTX infusion. Refer to Section 4.4.3 for admin guidelines. **Note age-based dosing**
High Dose Methotrexate (HD MTX)	IV over 24 hrs	5000 mg/m^2	1	Refer to Section 4.4.3, Section 5.9.1 & Appendix III for admin guidelines.
Leucovorin (LCV)	PO or IV	15 mg/m^2/dose	3-4	42, 48, and 54 hours after the start of HD MTX infusion. Refer to Section 4.4.3 & Appendix III for admin guidelines. For levoform the dose should be half.
Dexamethasone (DEX)	PO or IV	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day divided BID Refer to Section 4.4.3 for admin guidelines.
Vincristine (VCR)	IV push over 1 min*	1.5 1.5 mg/m^2/dose **Maximum dose: 2 mg** m1.5 g/ m^2/dose	1 & 6	*Or infusion via minibag as per institutional policy.
Cyclophosphamide (CPM)	IV over 30-60 min	200 mg/m^2/dose q12h	2-4	Administer every 12 hours x 5 doses. 1st dose immediately after completion of HDMTX. Refer to Section 4.4.3 for admin guidelines.
High Dose Cytarabine (HD ARAC)	IV over 3 hr	2000 mg/m^2/dose q12h	5	Administer every 12 hours x 2 doses Refer to Section 4.4.3 for admin guidelines.
PEG-L-Asparaginase (PEG-ASP)	IV over 1-2	2500 IU/ m^2/dose **Maximum dose: 3750 IU/m2**	5	Administer 3 hours following 2nd HD ARAC Refer to Section 4.4.3 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify: ……	……	……	5	Refer to Section 4.3.3
Filgrastim (G-CSF) or biosimilar	SubQ	5 mcg/kg/day	7-11	Administer until WBC≥ 3000/µL. Note additional dosages in comments box in Section 4.4.2 Refer to Section 4.4.3 for admin guidelines.

4.4.2 Therapy Delivery Map – Consolidation Block #1 SR Ph+ ALL Arm A (EsPhALL Arm)

Begin Consolidation therapy after recovery from Induction IB, after risk group and randomized treatment arm assigned, when starting criteria are met. Consolidation Block #1 therapy is 3 weeks (21 days).

_____ Patient ID number

_____ DOB

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	CPM ____mg	DEX ____mg ____mg	HD MTX ____mg	LCV ___mg	VCR ____mg	HD ARAC ____mg ____mg	PEG-ASP ____IU	Other L-ASP _____ IU	IT: MTX ____mg	ARAC ____mg	HC ___mg	G-CSF ____mcg	Studies
			Enter calculated dose above and actual dose administered below													
		1	____mg		____mg ____mg	____mg		____mg				___mg	___mg	___mg		a-e
		2		____mg	____mg ____mg											
		3		____mg	____mg ____mg											
		4		____mg	____mg ____mg		____mg									
		5			____mg ____mg				____mg ____mg	____mg						
		6						____mg								
		7													____mcg	
		8													____mcg	
		9													____mcg	
		10													____mcg	
		11													____mcg	
		21														
		22	Continue to Consolidation Block #2 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, and direct bilirubin ≤ 3 x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no greater than Grade 1 (whichever occurs later). Continue daily imatinib until Consolidation Block #2 begins. If the start of Consolidation Block #2 is delayed for 2 weeks due to myelosuppression (i.e. if myelosuppression persists 2 weeks after the end of Consolidation Block #1 chemotherapy), imatinib should be held, see Section 5.7.												

See Section 5.0 for Dose Modifications for Toxicities

4.4.3 Required Observations in Consolidation Block #1 SR Ph+ ALL Arm A (EsPhALL Arm)

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.4.4 Treatment Details for Consolidation Block #1 SR Ph+ ALL Arm A (EsPhALL Arm)

CONSENT TO POST-INDUCTION THERAPY (AND RANDOMIZATION FOR SR B-ALL PATIENTS) MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. SR PATIENTS WHO DECLINE TO BE RANDOMIZED ARE OFF PROTOCOL THERAPY.

Begin Consolidation Block #1 after risk group classification based on End Induction IB MRD is finalized and treatment arm has been assigned to Arm A. Consolidation Block #1should begin when peripheral counts recover to ANC ≥ 500/µL, platelets ≥ 50,000/µL, creatinine is within normal range for age, and direct bilirubin ≤ 3x Upper limit of normal (ULN), AST/ALT ≤ 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose, except of:

- **Vincristine, which is capped at a maximum dose of 2 mg**
- **Imatinib, which is capped at a maximum of 800 mg.**

Imatinib: Oral
Days: Daily
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Methotrexate/Cytarabine/Hydrocortisone (MAH): Intrathecal
Days: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	MTX: 8 mg, ARAC 20 mg, HC: 8 mg
2-2.99	MTX: 10 mg, ARAC 26 mg, HC 10 mg
≥ 3	MTX: 12 mg, ARAC 30 mg, HC: 12 mg

Give +/- 6 hours from start of HD MTX infusion.

High Dose Methotrexate: Intravenous over 24 hours
Day: 1
Dose: 5000 mg/m^2
Note: Administer 500 mg/ m^2 over 30 minutes, and the remaining 4500 mg/m^2 over 23.5 hours.

See Section 5.9.1 for hydration, leucovorin rescue and high dose methotrexate infusion guidelines.

Leucovorin: Oral or Intravenous. For levoform (instead of the racemic product) the dose should be half.

Days: 3-4

Dose: 15 mg/m^2/dose x minimum of 3 doses given at 42, 48, and 54 hours after the start of HD MTX infusion.

See Section 5.9.1 for hydration, leucovorin rescue and high dose methotrexate infusion guidelines.

Dexamethasone: Oral or Intravenous
Days: 1-5
Dose: 10 mg/m^2/dose BID; Total Daily dose: 20 mg/ m^2/day divided BID

Cyclophosphamide: Intravenous over 30-60 minutes
Days: 2 - 4
Dose: 200 mg/m^2/dose
Note: Administer IV every 12 hours x 5 doses, beginning on Day 2. First dose should be given immediately after completion of HD MTX infusion.

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Vincristine: Intravenous push or infusion via minibag per institutional policy
Days: 1 and 6
Dose: 1.5 mg/m^2/dose (maximum dose: 2mg)

High Dose Cytarabine: Intravenous over 3 hours
Day: 5
Dose: 2000 mg/m^2/dose
Note: Administer every 12 hours x 2 doses

Suggested premedications and supportive care: Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, administer artificial tears on an every 2-4 hour schedule.

PEG-L_Asparaginase: Intravenous over 1-2 hours.
Day: 5
Dose: 2500 International Units (IU)/m^2/dose
Note: Administer 3 hours after completion of 2nd High Dose Cytarabine. PEG-L_Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Filgrastim: Subcutaneous
Days: 7
Dose: 5mcg/kg/day
Note: Administer daily beginning anytime between days 7-11 until WBC ≥ 3000/µL. May substitute for Peg-filgrastim (100 mcg/kg) May substitute one-time dose of Peg-filgrastim (100 mcg/kg) for daily Filgrastim.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Consolidation Block #1, Consolidation Block #2 starts on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis no worse than Grade 1 (whichever occurs later).

4.5 Consolidation Block #2 SR Ph+ ALL Arm A (EsPhALL Arm)

4.5.1 Therapy Delivery Map – Consolidation Block #2 SR Ph+ ALL Arm A (EsPhALL Arm) Begin Consolidation therapy on Day 22 of Consolidation Block #1 or when criteria to start are met. Consolidation Block #2 therapy is 3 weeks (21 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.5.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, twice daily. See Section 4.5.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
High Dose Methotrexate (HD MTX)	IV	5000 mg/m^2	1	Refer to Section 4.5.3 & Appendix III for admin guidelines.
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	3-4	42, 48, and 54 hours after the start of HD MTX infusion. Refer to Section 4.5.3 & Appendix III for admin guidelines. For levoform the dose should be half.
Vincristine (VCR)	IV push over 1 min*	1.5 mg/m^2/dose **Maximum dose: 2 mg**	1 & 6	*Or infusion via minibag as per institutional policy Refer to Section 4.5.3 for admin guidelines
Dexamethasone (DEX)	PO or IV	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day divided BID Refer to Section 4.5.3 for admin guidelines.
Intrathecal MAH: Methotrexate (IT MTX) Cytarabine (IT ARAC) Hydrocortisone (IT HC)	IT	Age (yrs) / MTX / ARAC / HC 1-1.99 / 8 mg / 20mg / 8mg 2-2.99 / 10 mg / 26mg / 10mg ≥ 3 / 12 mg / 30 mg / 12mg	1	Administer ± 6 hours of the start of HDMTX infusion. Refer to Section 4.5.3 for admin guidelines. **Note age-based dosing**
Ifosfamide (IFOS)	IV over 1 hr	800 mg/m^2/dose	2-4	1st dose given immediately after HDMTX Q12hr x 5 doses. Refer to Section 4.5.3 for admin guidelines.
Mesna	IV	160 mg m^2/dose	2-4	Administer at hour 0, 4, and 8 from start of each ifosfamide infusion.
Daunorubicin (DAUN)	IV over 1-15 mins	30 mg/m^2/dose	5	Slow IV push of infusion over 1-15 minutes. May be infused over the course of 1 hour. Refer to Section 4.5.3 for admin guidelines.
PEG-L-Asparaginase (PEG-ASP)	IV over 1-2 hr	2500 IU/m^2/dose **Maximum dose 3750 UI/m2**	6	Refer to Section 4.5.3 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify: ….	.....	.....	6	Refer to Section 4.5.3 for admin guidelines.
Filgrastim (G-CSF) or biosimilar	SubQ	5 mcg/kg/day	7-11	Administer until WBC ≥ 3000/µL. Can use Peg-filgrastim, refer to Section 4.5.3 for admin guidelines

Continue to the next page for the therapy log.

4.5.2 Therapy Delivery Map – Consolidation Block #2 SR Ph+ ALL Arm A (EsPhALL Arm) Begin Consolidation therapy on Day 22 or when starting criteria is met. Consolidation Block #2 therapy is 3 weeks (21 days).	_____ Patient ID number _____ DOB

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Day	Imatinib ___mg	HD MTX ____mg	VCR ___mg	DEX ___mg ___mg	IT: MTX ARAC HC ___mg ____mg ___mg	IFOS ___mg ___mg	MESNA ____mg	LCV ___mg	DAUN ____mg	PEG-ASP ___IU	Other L-ASP _____ IU	G-CSF ____mcg	Studies
			Enter calculated dose above and actual dose administered below											
	1	____mg	____mg	___mg	___mg ___mg	___mg___mg___mg								a-e
	2				___mg ___mg		___mg ___mg	____mg ____mg ____mg ____mg ____mg ____mg						
	3				___mg ___mg ___mg ___mg		___mg ___mg	____mg ____mg ____mg ____mg ____mg ____mg	____mg ____mg					
	4						___mg	____mg ____mg ____mg	____mg					
	5				___mg ___mg					____mg				
	6			___mg							____IU			
	7												____mcg	
	8												____mcg	
	9												____mcg	
	10												____mcg	
	11												____mcg	
	21													
	22		Continue to Consolidation Block #3 on Day 22 or when peripheral counts recover to ANC ≥ 500/μL and platelets ≥ 50,000/μL, creatinine is within normal range for age, direct bilirubin ≤ 3 x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Continue daily imatinib until Consolidation Block #3 begins. If the start of Consolidation Block #3 is delayed for 2 weeks due to myelosuppression (i.e. if myelosuppression persists 2 weeks after the end of Consolidation Block #2 chemotherapy), imatinib should be held, see Section 5.7.											

See Section 5.0 for Dose Modifications for Toxicities

4.5.3 Required Observations in Consolidation Block #2 SR Ph+ALL Arm A (EsPhALL Arm)

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.5.4 Treatment Details for Consolidation Block #2 SR Ph+ ALL Arm A (EsPhALL Arm)

Begin Consolidation Block #2 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3 x upper limit of normal (ULN), AST/ALT ≤ 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg**
- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Methotrexate/Cytarabine/Hydrocortisone (MAH): Intrathecal
Days: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	MTX: 8 mg, ARAC 20 mg, HC: 8 mg
2-2.99	MTX: 10 mg, ARAC 26 mg, HC 10 mg
≥ 3	MTX: 12 mg, ARAC 30 mg, HC: 12 mg

Give +/- 6 hours from start of HD MTX infusion.

High Dose Methotrexate: Intravenous over 24 hours
Day: 1
Dose: 5000 mg/m^2
Note: Administer 500 mg/m^2 over 30 minutes, and the remaining 4500 mg/ m^2 over 23.5 hours.

See Section 5.9.1 for HD MTX/LCV rescue and infusion guidelines.

Leucovorin: Oral or Intravenous. For
Days: 3-4
Dose: 15 mg/$m^{2/}$dose x minimum of 3 doses given at 42, 48, and 54 hours after the start of HD MTX infusion.

Vincristine: Intravenous push or infusion via minibag per institutional policy

Days: 1 and 6

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

Dexamethasone: Oral or Intravenous
Days: 1-5
Dose: 10 mg/m^2/dose BID, Total Daily dose: 20 mg/m^2/day divided BID

Ifosfamide: Intravenous over 1 hour
Days: 2-4
Dose: 800 mg/m^2/dose Q12hours x5 doses
Note: Start immediately after the completion of HD MTX infusion.

Suggested hydration: from day 3, if HD MTX is cleared, administer 3,000 mL/m^2/day (125 mL/m^2/hour) using fluid containing D$_5$W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Monitor for adequate urine output as per institution guidelines. May use diuretics (e.g., furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Alternatively, rapid pre-hydration protocol may be used: Administer 750 mL/m^2 of 0.9% NaCL over 1 hour. Repeated measurements of urine specific gravity are not necessary with rapid pre-hydration.

Continuing hydration: D5W/0.45% NaCl, 100 mL/m^2/h until last mesna dose is finished.

Mesna: Intravenous
Days: 2-4
Dose: 160 mg/m^2/dose
Note: Administer at Hour 0, 4 and 8 from start of each ifosfamide dose.

The total dose of mesna to be administered with each dose of ifosfamide (480 mg/m2) can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as each ifosfamide dose and finished no sooner than 8 hours after the end of the ifosfamide infusion.

Daunorubicin: Intravenous over 1-15 minutes
Day: 5
Dose: 30 mg/m^2/dose
Note: May be administeredIV push or over 15-60 minutes per institutional guidelines.

PEG-L-Asparaginase: Intravenous over 1-2 hours
Day: 6
Dose: 2500 International Units/m^2/dose

Note: PEG-L_Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-

Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Filgrastim or biosimilar**: Subcutaneous**
Days: 7
Dose: 5mcg/kg/day
Note: Administer daily beginning anytime between Days 7-11 until WBC ≥ 3000/µL. May substitute one time dose of Pegfilgrastim (100 mcg/kg [maximum 6 mg] x 1 dose) for daily Filgrastim or biosimilar.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Consolidation Block #2, begin Consolidation Block #3 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.6 Consolidation Block #3 SR Ph+ ALL Arm A (EsPhALL Arm)

4.6.1 Therapy Delivery Map – Consolidation Block #3 SR Ph+ ALL Arm A (EsPhALL Arm)

Begin Consolidation therapy on Day 22 of Consolidation Block #2 or when criteria to start are met. Consolidation Block #3 therapy is 3 weeks (21 days).

_____ Patient ID number

_____ DOB

Treatment details and criteria to start are in Section 4.6.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.6.4 for details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	2000 mg/m^2	1-3	Q 12 hrs x 4 doses, refer to Section 4.6.3 for admin guidelines.
Dexamethasone (DEX)	PO or IV	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day divided BID. Refer to Section 4.6.3 for admin guidelines.
Etoposide (ETOP)	IV over 1-2 hrs	100 mg/m^2/dose	3-5	Q 12 hrs x 5 doses, refer to Section 4.6.3 for admin guidelines.
Intrathecal MAH: Methotrexate (IT MTX) Cytarabine (IT ARAC) Hydrocortisone (IT HC)	IT	Age (yrs) / MTX / ARAC / HC 1-1.99 / 8 mg / 20mg / 8mg 2-2.99 / 10 mg / 26mg / 10mg ≥ 3 / 12 mg / 30 mg / 12mg	5	Refer to Section 4.6.3 for admin guidelines. **Note age-based dosing**
PEG- L-asparaginase (PEG-ASP)	IV over 1-2 hrs	2500 IU/ m^2/dose **Maximum dose 3750 UI/m2**	6	Refer to Section 4.6.3 for admin guidelines.
If PEG-L-Asp at different dose or other product specify:.....	…….	……	6	Refer to Section 4.6.3 for admin guidelines.
Filgrastim (G-CSF) or biosimilar	SubQ	5 mcg/kg/day	7-11	Administer until WBC≥ 3000/µL. May use Peg-filgrastim, refer to Section 4.6.3 for admin guidelines.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ___mg	HD ARAC ____mg	DEX ___mg ___mg	ETOP ___mg ___mg	IT: MTX ARAC HC ____mg ____mg ____mg	PEG-ASP ___IU	Other L-ASP ___IU	G-CSF ____mcg	Studies
				Enter calculated dose above and actual dose administered below							
		1	____mg	____mg	___mg ___mg						a-d
		2		____mg ____mg	___mg ___mg						
		3		____mg	___mg ___mg	___mg ___mg					
		4			___mg ___mg	___mg ___mg					
		5			___mg ___mg	___mg	___mg ___mg ___mg				e
		6						____IU			
		7								____mcg	
		8								____mcg	
		9								____mcg	
		10								____mcg	
		11								____mcg	
		21									
		22	Begin Delayed Intensification #1 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10 ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Continue daily imatinib until Delayed Intensification #1 begins. If the start of Delayed Intensification #1 is delayed for 2 weeks due to myelosuppression (i.e. if myelosuppression persists 2 weeks after the end of Consolidation Block #3 chemotherapy), imatinib should be held, see Section 5.7.								

See Section 5.0 for Dose Modifications for Toxicities

a. Physical Exam b. Height, weight c. CBC with diff/platelets d. Bilirubin, AST, ALT, and creatinine e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.6.3 Treatment Details for Consolidation Block #3 SR Ph+ ALL Arm A (EsPhALL Arm)

Begin Consolidation Block #3 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

High Dose Cytarabine: Intravenous over 3 hours
Day: 1-2
Dose: 2000 mg/m^2/dose
Note: Administer every 12 hours x 4 doses

Suggested premedications and supportive care: Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2-4 hour schedule.

Dexamethasone: Oral or Intravenous
Days: 1-5
Dose: 10 mg/m^2/dose BID, Total Daily dose: 20 mg/m^2/day divided BID

Etoposide: Intravenous over 1-2 hours
Days: 3-6
Dose: 100 mg/m^2/dose
Note: Administer every 12 hours x 5 doses
The first dose of etoposide should be given approximately 12 hours after the start of the 4th dose of high dose cytarabine.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D_5W Avoid use of large volumes of D_5W due to potential development of hyponatremia. (Recommended concentration: 0,2-0,4 mg/ml).

Methotrexate/Cytarabine/Hydrocortisone (MAH): Intrathecal
Days: 5
Age-based dosing:

Age (yrs)	Dose
1-1.99	MTX: 8 mg, ARAC 20 mg, HC: 8 mg
2-2.99	MTX: 10 mg, ARAC 26 mg, HC 10 mg
≥ 3	MTX: 12 mg, ARAC 30 mg, HC: 12 mg

PEG-Asparaginase: Intravenous over 1-2 hours
Day: 6
Dose: 2500 International Units/m^2/dose

Note: Administer 3 hours after completion of 2nd High Dose Cytarabine. PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Filgrastim or biosimilar**: Subcutaneous**
Days: 7
Dose: 5mcg/kg/day
Note: Administer daily beginning anytime between Day 7-11 until WBC ≥ 3000/µL. May substitute one-time dose of Pegfilgrastim (100 mcg/kg [maximum 6 mg] x 1 dose) for daily Filgrastim or biosimilar.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Consolidation Block #3, Delayed Intensification starts on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.7 Delayed Intensification #1 SR Ph+ ALL Arm A (EsPhALL Arm)

4.7.1 Therapy Delivery Map – Delayed Intensification Part 1 SR Ph+ ALL Arm A (EsPhALL Arm) Begin DI Part 1 therapy on Day 22 of Consolidation Block #3 or when criteria to start are met. Delayed Intensification is 9 weeks (63 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.7.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.7.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	1	Refer to Section 4.7.4 for admin guidelines. **Note age-based dosing.**
Dexamethasone (DEX)	PO or IV	5 mg/m^2/day BID	1-7 & 15-21	Total daily dose: 10 mg/m^2/day divided BID Refer to Section 4.7.4 for admin guidelines.
Vincristine (VCR)	IV over 1 min	1.5 mg/m^2/dose **Maximum dose: 2 mg**	8, 15, 22 & 29	Or infusion via minibag as per institutional policy
Doxorubicin (DOXO)	IV over 1-15 min	25 mg/m^2/dose	8, 15, 22 & 29	Refer to Section 4.7.4 for admin guidelines. Slow IV push or IV bolus up to 1 hr per institutional guidelines.
PEG-L-Asparaginase (PEG-ASP)	IV over 1-2 hr	2500 IU/ m^2/dose **Maximum dose 3750 UI/m2**	8	Refer to Section 4.7.4 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify ……	……	……	8	Refer to Section 4.7.4 for admin guidelines.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	IT MTX ____mg	DEX ____mg	VCR ____mg	DOXO ____mg	PEG-ASP ____IU	Other L-ASP _____ IU	Studies
			Enter calculated dose above and actual dose administered below							
		1	____mg	____mg	____mg ____mg					a-e
		2			____mg ____mg					
		3			____mg ____mg					
		4			____mg ____mg					
		5			____mg ____mg					
		6			____mg ____mg					
		7			____mg ____mg					
		8				____mg	____mg	____mg		
		14								
		15			____mg ____mg	____mg	____mg			b
		16			____mg ____mg					
		17			____mg ____mg					
		18			____mg ____mg					
		19			____mg ____mg					
		20			____mg ____mg					
		21			____mg ____mg					
		22				____mg	____mg			
		28								
		29				____mg	____mg			a-d
		35		Continue to DI Part 2 (Day 36-49) on the next page. Continue daily imatinib until DI Part 2 begins.						

See Section 5.0 for Dose Modifications for Toxicities.

4.7.2 Therapy Delivery Map – Delayed Intensification Part 2 SR Ph+ ALL Arm A (EsPhALL Arm) Begin DI Part 2 therapy on Day 36 or when criteria to start are met.	_____ _____ Patient ID number DOB

Delayed Intensification therapy is 9 weeks (63 days). Treatment details and criteria to start are in Section 4.7.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	Daily	Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	36	Refer to Section 4.7.4 for admin guidelines.
Thioguanine (TG)	PO	60 mg/m^2/day	36-49	Refer to Section 4.7.4 for admin guidelines.
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose	38-41 & 45-48	Refer to Section 4.7.4 for admin guidelines. Must have **ANC ≥ 300/µL** and **platelets ≥ 30,000/uL** to start each 4-day Cytarabine block.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1-1.99 / 8 mg 2-2.99 / 10 mg ≥ 3 / 12 mg	38 & 45	Refer to Section 4.7.4 for admin guidelines. **Note age-based dosing.**

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	CPM ____mg	TG ____mg	ARAC ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below					
		36	____mg	____mg	____mg	____mg	____mg	e
		37				mg		
		38				____mg		
		39				____mg		
		43				____mg	____mg	e
		44				____mg		
		45				____mg		
		46				____mg		
		49						
		64	Begin Interim Maintenance on Day 64 when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age and direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no greater than Grade 1 or when criteria to start are met (whichever occurs later). Continue daily imatinib until Interim Maintenance begins. If the start of Interim Maintenance is delayed for 2 weeks due to myelosuppression (i.e. if myelosuppression persists 2 weeks after the end of Delayed Intensification chemotherapy), imatinib should be held, see Section 5.7.					

See Section 5.0 for Dose Modifications for Toxicities.

4.7.3 Required Observations in Delayed Intensification #1 SR Ph+ ALL Arm A (EsPhALL Arm)

a. Physical exam b. Height, weight c. CBC with diff/platelets d. Bilirubin, AST, ALT, and creatinine e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.7.4 Treatment Details for Delayed Intensification #1 SR Ph+ ALL Arm A (EsPhALL Arm)

Delayed Intensification #1 is given in 2 parts.

Begin Delayed Intensification #1 Part 1 on Day 22 after Consolidation Block #3 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Once Delayed Intensification Part 1 begins, interrupt only for severe infection and/or major clinical concern.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Methotrexate: Intrathecal
Day: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Dexamethasone: Oral or Intravenous
Days: 1-7 and 15-21
Dose: 5 mg/ m^2/dose BID, Total Daily dose: 10 mg/ m^2/day divided BID

Vincristine: Intravenous push or infusion via minibag per institutional policy
Days: 8, 15, 22 and 29
Dose: 1.5 mg/ m^2/dose (maximum dose: 2mg)

Doxorubicin: Slow intravenous push over 1-15 minutes or intravenous bolus up to 1 hour per institutional guidelines

Days: 8, 15, 22 and 29
Dose: 25 mg/ m^2/dose

PEG-L-Asparaginase: Intravenous over 1-2 hours
Day: 8
Dose: 2500 International Units/m^2/dose

Note: PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Criteria to start Delayed Intensification #1 Part 2
Begin Delayed Intensification #1 Pt. 2 on Day 36 or when peripheral counts recover to ANC > 500/µL and platelets > 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3 x Upper limit of normal (ULN), AST/ALT ≤ 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Once Delayed Intensification Part 2 begins, interrupt only for severe infection and/or major clinical concern.
.

Imatinib: Oral
Days: Daily
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

Cyclophosphamide: Intravenous over 30-60 minutes
Day: 36
Dose: 1000 mg/ m^2/dose
Note: Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: **Oral**

Days: 36-49
Dose: 60 mg/ m2/day

Note: Administer once daily by mouth in the evening on an empty stomach. If taken by tablet, daily doses should be spread as evenly as possible so that the

total weekly dose is 420 mg/ m2/day, and the cumulative 14-day dose is 840 mg/ m^2/day. Refer to Appendix V for details.

Methotrexate: Intrathecal
Days: 38 and 45
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Cytarabine: Intravenous over 1-30 minutes or subcutaneous
Days: 38-41 and 45-48
Dose: 75 mg/m^2/dose

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Delayed Intensification #1, Interim Maintenance starts at least 14 days from Day 49 of the Delayed Intensification phase or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.8 Interim Maintenance SR Ph+ ALL Arm A (EsPhALL Arm)

4.8.1 Therapy Delivery Map – EsPhALL Interim Maintenance SR Ph+ ALL Arm A (EsPhALL Arm) Begin Interim Maintenance therapy on Day 64 of Delayed Intensification or when criteria to start are met. Interim Maintenance therapy is 4 weeks (28 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.8.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.8.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/ m^2/day	1, 8, 15, & 22	
Mercaptopurine (MP)	PO	50 mg/ m^2/day	1-28	Refer to Section 4.8.3. & Appendix IV for admin guidelines. .
For patients with CNS3 disease cranial XRT (See Section 4.8.3. & 16.0) should begin on Day 1 of Interim Maintenance therapy and should be completed by Day 14.				

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	Studies
			Enter calculated dose above and actual dose administered below			
		1	____mg	____mg	____mg	a-d
		2				
		3				
		4				
		5				
		6				
		7				
		8		____mg		
		15		____mg		
		16				
		17				
		18				
		19				
		20				
		21				
		22		____mg		
		28				
		29	Begin Delayed Intensification #2 on Day 29 or when peripheral counts recover to ANC ≥ 500/μL and platelets ≥ 50,000/μL, and creatinine is within normal range for age, direct bilirubin ≤ 3x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). If the start of Delayed Intensification #2 is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.			

See Section 5.0 for Dose Modifications for Toxicities

4.8.2 Required Observations in Interim Maintenance SR Ph+ ALL Arm A (EsPhALL Arm)

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT and Creatinine

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.8.3 Treatment Details for Interim Maintenance SR Ph+ ALL Arm A (EsPhALL Arm)

Begin EsPhALL Interim Maintenance on Day 64 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

CNS Radiation Therapy

Patients with CNS3 disease at diagnosis will receive cranial irradiation, 1800cGy in 10 fractions, during the first week of Interim Maintenance therapy, and should be completed within 14 days of starting. See Section 16.0 for details pertaining to cranial irradiation.

Imatinib: Oral
Days: Daily
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg. Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7). See Appendix VI for details.

Methotrexate: Oral
Days: 1, 8, 15, and 22
Dose: 20 mg/ m^2/day

Mercaptopurine: Oral
Days: 1-28
Dose: 50 mg/ m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m2 (28-day cumulative dose is 1400 mg/m^2).
See Appendix IV for details.
It is strongly recommended that mercaptopurine be taken at the same time each day.
See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status.

Following completion of Interim Maintenance, Delayed Intensification #2 starts on Day 29 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.9 Delayed Intensification #2 SR Ph+ ALL Arm A (EsPhALL Arm)

4.9.1Therapy Delivery Map – Delayed Intensification #2 Part 1 SR Ph+ ALL Arm A (EsPhALL Arm) Begin DI #2 Part 1 therapy on Day 29 or when criteria to start are met. Delayed Intensification therapy is 7 weeks (49 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.9.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.9.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	1	Refer to Section 4.9.4 for admin guidelines. **Note age-based dosing.**
Dexamethasone (DEX)	PO or IV	5 mg/m^2/day BID	1-7 & 15-21	Total daily dose: 10 mg/m^2/day divided BID Refer to Section 4.9.4 for admin guidelines.
Vincristine (VCR)*	IV over 1 min	1.5 mg/m^2/dose **Maximum dose: 2 mg**	8, 15, 22 & 29	*Or infusion via minibag as per institutional policy
Doxorubicin (DOXO)	IV over 1-15 min	25 mg/m^2/dose	8, 15, 22 & 29	Slow IV push or IV bolus up to 1 hr per institutional guidelines. Refer to Section 4.9.4 for admin guidelines.
PEG-L-Asparaginase (PEG-ASP)	IV over 1-2 hr	2500 IU/ m^2/dose **Maximum dose: 3750 UI/m2**	8	Refer to Section 4.9.4 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify ……..	…….	……	8	Refer to Section 4.9.4 for admin guidelines.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	IT MTX ____mg	DEX ____mg ____mg	VCR ____mg	DXR ____mg	DOXO ____mg	PEG-ASP ____IU	OTHER L-Asp _____IU	Studies
				Enter calculated dose above and actual dose administered below							
		1	____mg	____mg	____mg ____mg			____mg			a-e
		2			____mg ____mg						
		3			____mg ____mg						
		4			____mg ____mg						
		5			____mg ____mg						
		6			____mg ____mg						
		7			____mg ____mg						
		8				____mg	____mg	____mg	____IU		
		15			____mg ____mg	____mg	____mg	____mg			
		16			____mg ____mg						
		17			____mg ____mg						
		18			____mg ____mg						
		19			____mg ____mg						
		20			____mg ____mg						
		21			____mg ____mg						
		22				____mg	____mg	____mg			
		28									
		29				____mg	____mg	____mg			a-d
		35		Continue to DI Part 2 (Day 36-49) on the next page. Continue daily imatinib until DI Part 2 begins.							

See Section 5.0 for Dose Modifications for Toxicities.

4.9.2Therapy Delivery Map – Delayed Intensification #2 Part 2 SR Ph+ ALL Arm A (EsPhALL Arm) Begin DI #2 Part 2 therapy on Day 36 or when criteria to start are met. Delayed Intensification therapy is 7 weeks (49 days).	_____ _____ Patient ID number DOB

Treatment details and criteria to start are in Section 4.9.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	36	Refer to Section 4.9.4 for admin guidelines.
Thioguanine (TG)	PO	60 mg/m^2/day	36-49	Refer to Section 4.9.4 for admin guidelines.
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose	38-41 & 45-48	Refer to Section 4.9.4 for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	38 & 45	Refer to Section 4.9.4 for admin guidelines. **Note age-based dosing.**

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	TG ____mg	CPM ____mg	ARAC ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below					
		36	____mg	____mg	____mg	____mg	____mg	e
		37	↓	↓		____mg		
		38				____mg		
		39				____mg		
		43				mg	mg	e
		44				mg		
		45				____mg		
		46				____mg		
		49						
		50	Begin Maintenance on Day 50 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Continue daily imatinib until Interim Maintenance begins. If the start of Maintenance Cycle 1 is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.					

See Section 5.0 for Dose Modifications for Toxicities.

a. Physical exam b. Height, weight c. CBC with diff/platelets d. Bilirubin, AST, ALT, and creatinine e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.9.4 Treatment Details for Delayed Intensification #2 SR Ph+ALL Arm A (EsPhALL Arm)

Delayed Intensification #2 is given in 2 parts.

Begin Delayed Intensification #2 Part 1 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Once Delayed Intensification Part 1 begins, interrupt only for severe infection and/or major clinical concern.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Methotrexate: Intrathecal
Day: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Dexamethasone: Oral or Intravenous
Days: 1-7 and 15-21
Dose: 5 mg/ m^2/dose BID, Total Daily dose: 10 mg/ m^2/day divided BID

Vincristine: Intravenous push or infusion via minibag per institutional policy
Days: 8, 15, 22 and 29
Dose: 1.5 mg/ m2/dose (maximum dose: 2mg)

Doxorubicin: Slow intravenous push over 1-15 minutes or Intravenous bolus up to 1 hour per institutional guidelines
Days: 8, 15, 22 and 29
Dose: 25 mg/m^2/dose

PEG-L-Asparaginase: Intravenously over 1-2 hours
Day: 8
Dose: 2500 International Units/m^2/dose

PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Delayed Intensification #2 Part 2
Begin Delayed Intensification #2 Part 2 on Day 36 or when peripheral counts recover with ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3 x upper limit of normal (ULN), AST/ALT < 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Once Delayed Intensification Part 1 begins, interrupt only for severe infection and/or major clinical concern.

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

Cyclophosphamide: Intravenous over 30-60 minutes
Day: 36
Dose: 1000 mg/ m^2/dose
Note: Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion

Thioguanine: Oral
Days: 36-49
Dose: 60 mg/ m2/day

Note: Administer once daily by mouth in the evening on an empty stomach. If taken by tablet, daily doses should be spread as evenly as possible so that the total weekly dose is 420 mg/ m2/day, and the cumulative 14-day dose is 840 mg/ m^2/day. Refer to Appendix V for details.

Methotrexate: Intrathecal
Days: 38 and 45
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Cytarabine: Intravenous over 1-30 minutes or Subcutaneous
Days: 38-41 and 45-48
Dose: 75 mg/m^2/dose

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Delayed Intensification #2, being Maintenance on Day 50 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.10 Maintenance Cycle 1 SR Ph+ALL Arm A (EsPhALL Arm)

4.10.1 Therapy Delivery Map –Maintenance Cycle 1 SR Ph+ ALL Arm A (EsPhALL Arm) Begin Maintenance therapy on Day 50 of DI #2 or when criteria to start are met.	_____ _____ Patient ID number DOB

Extensive details and criteria to start are in Section 4.10.3 (treatment overview).

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.10.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/day	Once weekly	Refer to Section 4.10.3
Mercaptopurine (MP)	PO	50 mg/m^2/day	1-84	Refer to Section 4.10.3 & Appendix IV for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 MTX 8 mg 2-2.99 MTX 10 mg ≥ 3 MTX 12 mg	1 & 43	Note: Administer once every 6 weeks, 6 total doses during the first three cycles of maintenance. Discontinue after 6th dose. *Do not administer to CNS3 patients who received cranial radiation. Refer to Section 4.10.3 for admin guidelines.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below				
		1	____mg	____mg	____mg	____mg*	a-e
		8		____mg			
		15		____mg			
		22		____mg			
		29		____mg			a-d
		36		____mg			
		43		____mg		____mg*	e
		50		____mg			
		57		____mg			a-d
		64		____mg			
		71		____mg			
		78		____mg			
		84					
		85	Continue Maintenance therapy Cycle 2 Section 4.11. If the start of Maintenance Cycle 2 is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.				

See Section 5.0 for Dose Modifications for Toxicities

4.10.2 Required Observations in Maintenance Cycle 1 SR Ph+ ALL Arm A (EsPhALL Arm)

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)
e. CSF cell count, cytospin with each IT

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.10.3 Treatment Details for Maintenance Cycle 1 SR Ph+ ALL Arm A (EsPhALL Arm)

Begin Maintenance therapy on Day 50 of Delayed Intensification or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). All treatment oral and intrathecal will be interrupted for myelosuppression as outlined in Section 5.11.Imatinib will be delivered as scheduled, despite myelosuppression.

The administration schedule describes the 12-week cycle of Maintenance therapy Cycle 1.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 50 mg/ m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m^2. See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status

Methotrexate: Oral
Days: 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78
Dose: 20 mg/ m^2/dose

Methotrexate: Intrathecal
Day: 1 & 43
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Note: IT MTX is not given during Maintenance in CNS3 patients who received cranial radiation.

Research Studies
For patients who consent submit a bone marrow sample for MRD testing. Refer to Section 14.1 for details.

See Section 5.0 for Dose Modifications based on Toxicities.

Following the completion of Maintenance therapy Cycle 1, continue onto Maintenance therapy Cycle 2 in Section 4.11.

4.11 Maintenance Cycle 2 SR Ph+ ALL Arm A (EsPhALL Arm)

4.11.1. Therapy Delivery Map –Maintenance Cycle 2 SR B-ALL Arm A (EsPhALL Arm)

Begin Maintenance therapy on Day 85 of Maintenance therapy Cycle 1 or when criteria to start are met.

_____ _____
Patient ID number DOB

Treatment details and criteria to start are in Section 4.11.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.11.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/dose	Once weekly	Refer to Section 4.11.3
Mercaptopurine (MP)	PO	50 mg/m^2/day	1-84	Refer to Section 4.11.3 & Appendix IV for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 MTX 8 mg 2-2.99 MTX 10 mg ≥ 3 MTX 12 mg	1 & 43	Note: Administer once every 6 weeks, 6 total doses during Cycle 1 and 2. Discontinue after 6th dose. *Do not administer to CNS3 patients who received cranial radiation. Refer to Section 4.11.3 for admin guidelines.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below				
		1	____mg	____mg	____mg	____mg*	a-e
		8		____mg			
		15		____mg			
		22		____mg			
		29		____mg			a-d
		36		____mg			
		43		____mg		____mg*	e
		50		____mg			
		57		____mg			a-d
		64		____mg			
		71		____mg			
		78		____mg			
		84		____mg			
		85	Continue Maintenance therapy Cycle 3 in Section 4.12. If the start of Inerim Maintenance Cycle 3 is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.				

See Section 5.0 for Dose Modifications for Toxicities.

4.11.2 Required Observations in Maintenance Cycle 2 SR Ph+ ALL Arm A (EsPhALL Arm)

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)
e. CSF cell count, cytospin with each IT

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.11.3 Treatment Details for Maintenance Cycle 2 SR Ph+ ALL Arm A (EsPhALL Arm)

Begin Maintenance therapy Cycle 2 on Day 85 of the previous Maintenance cycle. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). All treatment oral and intrathecal will be interrupted for myelosuppression as outlined in Section 5.11.Imatinib will be delivered as scheduled, despite myelosuppression.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

The administration schedule describes the 12-week cycle of Maintenance therapy Cycle 2.

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 50 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m^2. See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status.

Methotrexate: Oral
Days: 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78
Dose: 20 mg/m^2/dose

Methotrexate: Intrathecal
Day: 1 & 43
Note: Administer once every 6 weeks, 6 total doses. Discontinue after 6th dose.
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Note: IT MTX is not given during Maintenance in CNS3 patients who received cranial radiation.

See Section 5.0 for Dose Modifications based on Toxicities.

Following the completion of Maintenance Therapy Cycle 2, continue onto Maintenance Therapy Cycle 3 in Section 4.12.

4.12 Maintenance Cycle 3 SR Ph+ ALL Arm A (EsPhALL Arm)

4.12.1 Therapy Delivery Map –Maintenance Cycle 3 SR Ph+ ALL Arm A (EsPhALL Arm) Begin Maintenance therapy on Day 85 of Maintenance therapy Cycle 2 or when criteria to start are met.	_____ _____ Patient ID number DOB

Treatment details and criteria to start are in Section 4.12.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.12.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/day	Once weekly	Refer to Section 4.12.3
Mercaptopurine (MP)	PO	50 mg/m^2/day	1-84	Refer to Section 4.12.3 & Appendix IV for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 MTX 8 mg 2-2.99 MTX 10 mg ≥ 3 MTX 12 mg	1 & 43	Administer once every 6 weeks, 6 total doses. Discontinue after 6th dose. *Do not administer to CNS3 patients who received cranial radiation. Refer to Section 4.12.3 for admin guidelines.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below				
		1	____mg	____mg	____mg	____mg*	a-e
		8		____mg			
		15		____mg			
		22		____mg			
		29		____mg			a-d
		36		____mg			
		43		____mg		____mg*	e
		50		____mg			
		57		____mg			a-d
		64		____mg			
		71		____mg			
		78		____mg			
		84					
		85	Continue Maintenance therapy Cycle 4 in Section 4.13. If the start of Maintenance Cycle 4 is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.				

See Section 5.0 for Dose Modifications for Toxicities.

4.12.2 Required Observations in Maintenance Cycle 3 SR Ph+ ALL Arm A (EsPhALL Arm)

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)
e. CSF cell count, cytospin with each IT

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.12.3 Treatment Details for Maintenance Cycle 3 SR Ph+ ALL Arm A (EsPhALL Arm)

Begin Maintenance therapy Cycle 3 on Day 85 of the previous Maintenance cycle. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). All treatment oral and intrathecal will be interrupted for myelosuppression as outlined in Section 5.11.Imatinib will be delivered as scheduled, despite myelosuppression.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

The administration schedule describes the 12-week cycle of Maintenance therapy Cycle 3.

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 50 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m^2. See Appendix IV for details.

See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day.

Methotrexate: Oral
Days: 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78
Dose: 20 mg/m^2/day

Methotrexate: Intrathecal
Day: 1 and 43
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Note: IT MTX is not given during Maintenance in CNS3 patients who received cranial radiation.

See Section 5.0 for Dose Modifications based on Toxicities.

Following the completion of Maintenance Therapy Cycle 3, continue onto Maintenance Therapy Cycle 4 in Section 4.13.

4.13 Maintenance Cycle 4 and Subsequent Cycles SR Ph+ ALL Arm A (EsPhALL Arm)

4.13.1 Therapy Delivery Map –Maintenance Cycle 4 and Subsequent Cycles SR B-ALL Arm A (EsPhALL Arm) Begin Maintenance therapy on Day 85 of Maintenance therapy Cycle 3 or when criteria to start are met.	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.13.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.13.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/dose	Once weekly	Refer to Section 4.13.3.
Mercaptopurine (MP)	PO	50 mg/m^2/day	1-84	Refer to Section 4.13.3. & Appendix IV for admin guidelines.

Enter Cycle #: _____ **Ht _____cm** **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	Studies
			Enter calculated dose above and actual dose administered below			
		1	____mg	____mg	____mg	a-d
		8		____mg		
		15		____mg		
		22		____mg		
		29		____mg		a-d
		35		____mg		
		42		____mg		
		49		____mg		
		56		____mg		a-d
		63		____mg		
		70		____mg		
		77		____mg		
		84		____mg		
		85	Continue Maintenance therapy throughout 2 years from the start of protocol therapy, Induction IA. If continued Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.			

See Section 5.0 for Dose Modifications for Toxicities.

4.13.2 Required Observations in Maintenance Cycle 4 and Subsequent Cycles SR Ph+ ALL Arm A (EsPhALL Arm)

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.13.3 Treatment Details for Maintenance Cycle 4 and Subsequent Cycles
SR Ph+ ALL Arm A (EsPhALL Arm)

Begin Maintenance therapy on Day 85 of the previous Maintenance cycle. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). Oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.11. Imatinib will be delivered as scheduled, despite myelosuppression.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

Maintenance consist of 12-week cycles repeated until total duration of therapy is 2 years from the start of Induction IA. The administration schedule describes one 12-week cycle of Maintenance therapy.

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 50 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m^2. See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

See Section 5.10 for suggested starting dose based on TPMT and NUDT15 status.

Methotrexate: Oral
Days: 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78
Dose: 20 mg/ m^2/dose

See Section 5.0 for Dose Modifications based on Toxicities.

Total duration of therapy should be 2 years (104 weeks) from the start of Induction IA therapy.

4.14 HD MTX Interim Maintenance SR Ph+ALL Arm B (Investigational COG Arm)

4.14.1 Therapy Delivery Map – HD MTX Interim Maintenance SR Ph+ALL Arm B (Investigational COG Arm) Begin HD MTX Interim Maintenance therapy after recovery from Induction IB, after risk group and randomized treatment arm assigned, when criteria to start are met. HD MTX Interim Maintenance therapy is 9 weeks (63 days).	_____ _____ Patient ID number DOB

Treatment details and criteria to start are in Section 4.14.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.14.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Vincristine (VCR)	IV over 1 min*	1.5 mg/m^2/dose **Maximum dose: 2 mg**	1, 15, 29 & 43	*Or infusion via minibag as per institutional policy.
High Dose Methotrexate (HD MTX)	IV	5000 mg/m^2/dose	1, 15, 29 & 43	Refer to Section 4.14.3 & Appendix III for admin guidelines.
Leucovorin (LCV)	PO or IV	15 mg/m^2/dose	3-4; 17-18; 31-32; 45-46	Refer to Section 4.14.3 for admin guidelines. 42, 48, and 54 hours after the start of HD MTX infusion. For levoform dose should be half.
Mercaptopurine (MP)	PO	25 mg/m^2/day	1-56	Refer to Section 4.14.3 for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1-1.99 / 8 mg 2-2.99 / 10 mg ≥ 3 / 12 mg	1 & 29	Age based dosing.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	VCR ____mg	HD MTX ____mg	LCV ____mg	MP ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below						
		1	____mg	____mg	____mg		____mg	____mg	a-e
		3				____mg			
		4				____mg ____mg			
		15		____mg	____mg				a, c, d
		17				____mg			
		18				____mg ____mg			
		29		____mg	____mg			____mg	a, c-e
		31				____mg			
		32				____mg ____mg			
		43		____mg	____mg				a, c, d
		44				____mg			
		45				____mg ____mg			
		56							
		64	Begin Delayed Intensification on Day 64 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Continue daily imatinib until Delayed Intensification begins. If the start of Delayed Intensifcation #1 is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.						

See Section 5.0 for Dose Modifications for Toxicities.

4.14.2 Required Observations in HD MTX Interim Maintenance SR Ph+ ALL Arm B (Investigational COG Arm)

a. Physical exam
b. Height, weight
c. CBC with diff/platelets. Collect on Day 1 and prior to each HD MTX dose.
d. Bilirubin, AST/ALT and creatinine. Collect on Day 1 and prior to each HD MTX dose.
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.14.3 Treatment Details for HD MTX Interim Maintenance SR Ph+ ALL Arm B (Investigational COG Arm)

CONSENT TO POST-INDUCTION THERAPY (AND RANDOMIZATION FOR SR B-ALL PATIENTS) MUST TAKE PLACE BEFORE STARTING INTERIM MAINTENANCE #1, AFTER RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. SR PATIENTS WHO DECLINE TO BE RANDOMIZED ARE OFF PROTOCOL THERAPY.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

Begin HD MTX Interim Maintenance #1 after risk group classification based on End Induction IB MRD is finalized, and treatment arm has been assigned to the **Arm B (Investigational COG Arm)**. ND MTX Interim Maintenance #1 should begin when peripheral counts recover to ANC ≥ 500/μL and platelets ≥ 50,000/μL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Vincristine: Intravenous push or infusion via minibag per institutional policy
Days: 1, 15, 29 and 43
Dose: 1.5 mg/m2/dose (maximum dose: 2mg)

High Dose Methotrexate: Intravenous over 24 hours
Day: 1, 8, 29 and 43
Dose: 5000 mg/m^2/dose
Note: Administer 500 mg/ m^2 over 30 minutes, and the remaining 4500 mg/ m^2 over 23.5 hours.

See Section 5.9.1 for hydration, leucovorin rescue and high dose methotrexate infusion guidelines.

Leucovorin: Oral or Intravenous
Days: 3-4, 17-18, 31-32, 45-46.
Dose: 15 mg/m^2/dose x minimum of 3 doses given at 42, 48, and 54 hours after the start of HD MTX infusion. For levoform (instead of racemic) dose should be half.

See Section 5.9.1 for hydration, leucovorin rescue and high dose methotrexate infusion guidelines.

Mercaptopurine: Oral
Days: 1-56
Dose: 25 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 175 mg/m2 (56-day cumulative dose is 1400 mg/m^2).
See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

Methotrexate: Intrathecal
Days: 1 and 29
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Give +/- 6 hours from start of HD MTX infusion.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of HD MTX Interim Maintenance, Delayed Intensification starts on Day 64 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.15 Delayed Intensification SR Ph+ ALL Arm B (Investigational COG Arm)

4.15.1 Therapy Delivery Map – Delayed Intensification Part 1 SR Ph+ALL(Investigational COG Arm)

Begin DI Part 1 therapy on Day 64 after Interim Maintenance #1, or when criteria to start are met. Delayed Intensification therapy is 8 weeks (56 days).

_____ _____
Patient ID number DOB

Treatment details and criteria to start are in Section 4.15.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.15.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	1	Refer to Section 4.15.4 for admin guidelines. **Age-based dosing.**
Dexamethasone (DEX)	PO or IV	5 mg/m^2/dose BID	1-7 & 15-21	Total daily dose: 10 mg/m^2/day divided BID Refer to Section 4.15.4 for admin guidelines.
Vincristine (VCR)*	IV over 1 min*	1.5 mg/m^2/dose **Maximum dose: 2 mg**	1, 8 & 15	*Or infusion via minibag as per institutional policy
Doxorubicin (DOXO)	IV over 1-15 min	25 mg/m^2/dose	1, 8 & 15	Slow IV push or IV bolus up to 1 hr per institutional standards. Refer to Section 4.15.4 for admin guidelines.
PEG-L-Asparaginase (PEG-ASP)	IVover 1-2 hrs	2500 IU/m^2 **Maximum dose:3750 UI/m2**	4	Refer to Section 4.15.4 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify ……	……	……	4	Refer to Section 4.15.4 for admin guidelines.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	IT MTX ____mg	DEX ____mg ____mg	VCR ____mg	DOXO ____mg	PEG-ASP ____IU	Other L-ASP _____IU	Studies
			Enter calculated dose above and actual dose administered below							
		1	____mg	____mg	____mg ____mg	____mg	____mg			a-f
		2			____mg ____mg					
		3			____mg ____mg					
		4			____mg ____mg			____IU		
		5			____mg ____mg					
		6			____mg ____mg					
		7			____mg ____mg					
		8				____mg	____mg			
		15			____mg ____mg	____mg	____mg			
		16			____mg ____mg					
		17			____mg ____mg					
		18			____mg ____mg					
		19			____mg ____mg					
		20			____mg ____mg					
		21			____mg ____mg					
		22								
		28		Continue to DI Part 2 (Day 29-49) on the next page.						

See Section 5.0 for Dose Modifications for Toxicities.

4.15.2 Therapy Delivery Map – Delayed Intensification Part 2 SR Ph+ ALL Investigational COG Arm

Begin DI Part 2 therapy on Day 29 or when criteria to start are met. Delayed Intensification therapy is 8 weeks (56 days).

_____ _____
Patient ID number DOB

Treatment details and criteria to start are in Section 4.15.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	29	Refer to Section 4.15.4 for admin guidelines.
Thioguanine (TG)	PO	60 mg/m^2/day	29-42	Refer to Section 4.15.4 for admin guidelines.
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/day	29-42 & 36-39	Refer to Section 4.15.4for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1-1.99 / 8 mg 2-2.99 / 10 mg ≥ 3 / 12 mg	29 & 36	Refer to Section 4.15.4 for admin guidelines. **Age-based dosing.**
Vincristine (VCR)*	IV over 1 min	1.5 mg/ m2/dose Maximum dose: 2 mg	43 & 50	*Or infusion via minibag as per institutional policy
PEG-L-Asparaginase (PEG-ASP)	IV over 1-2 hrs	2500 IU/m^2/dose	43	Refer to Section 4.15.4 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify ……	…….	……	43	Refer to Section 4.15.4 for admin guidelines.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	CPM ____mg	TG ____mg	ARAC ____mg	IT MTX ____mg	VCR ____mg	PEG-ASP ____IU	Other L-ASP ----------IU	Studies
			Enter calculated dose above and actual dose administered below								
		29	____mg	____mg	____mg	____mg	____mg				a-e
		30				____mg					
		31				____mg					
		32				____mg					
		36				____mg	____mg				c, e
		37				____mg					
		38				____mg					
		39				____mg					
		40									
		41									
		42									
		43						____mg	____IU		c
		50						____mg			c
		64	Begin the next phase on Day 57 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Continue daily imatinib ntil Interim Maintenance #2 begins. If the start of Interim Maintenance is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.								

See Section 5.0 for Dose Modifications for Toxicities.

4.14.4 Required Observations in Delayed Intensification SR Ph+ ALL Arm B (Investigational COG Arm)

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.15.4 Treatment Details for Delayed Intensification SR Ph+ ALL Arm B (Investigational COG Arm)

Delayed Intensification is given in 2 parts

Begin Delayed Intensification Part 1 on Day 64 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Once Delayed Intensification Part 1 begins, interrupt only for severe infection and/or major clinical concern.
For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg. Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7). See Appendix VI for details.

Methotrexate: Intrathecal
Day: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Dexamethasone: Oral or Intravenous
Days: 1-7 and 15-21
Dose: 5 mg/m^2/dose BID, Total Daily dose: 10 mg/ m^2/day divided BID

Vincristine: Intravenous push or infusion via minibag per institutional policy
Days: 1, 8 and 15
Dose : 1.5 mg/m2/dose (maximum dose : 2mg)

Doxorubicin: Slow IV push over 1-15 minutes or IV bolus up to 1 hour per institutional guidelines
Days: 1, 8, and 15
Dose: 25 mg/m^2/dose

PEG-L-Asparaginase: Intravenous over 1-2 hours
Day: 4
Dose: 2500 International Units/m^2/dose
PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Criteria to start Delayed Intensification Part 2
Begin Delayed Intensification Pt. 2 on Day 29 or when peripheral counts recover with ANC > 500/µL and platelets > 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3 x upper limit of normal (ULN), AST/ALT ≤ 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Once Delayed Intensification Part 2 begins, interrupt only for severe infection and/or major clinical concern.

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

Cyclophosphamide: Intravenous over 30-60 minutes
Day: 29
Dose: 1000 mg/m^2/dose
Note: Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion

Thioguanine: Oral
Days: 29-42
Dose: 60 mg/m2/day
Note: Administer once daily by mouth in the evening on an empty stomach. If taken by tablet, daily doses should be spread as evenly as possible so that the total weekly dose is 420 mg/ m^2/day, and the cumulative 14-day dose is 840 mg/ m^2/day. See Appendix V for details.

Cytarabine: Intravenous over 1-30 minutes or Subcutaneous
Days: 29-32 and 36-39
Dose: 75 mg/m^2/dose
Note: Must have ANC ≥ 300/µL and platelets ≥ 30,000/uL to start the 4 -day Cytarabine block on Days 36.

Methotrexate: Intrathecal
Days: 29 and 36
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Vincristine: Intravenous push or infusion via minibag per institutional policy

Days: 43 and 50
Dose: 1.5 mg/m2/dose (maximum dose: 2mg)

PEG-L-Asparaginase: Intravenous over 1-2 hours
Day: 43
Dose: 2500 International Units/m^2/dose
PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Delayed Intensification, begin Capizzi Interim Maintenance on Day 57 of the Delayed Intensification phase or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.16 Capizzi MTX Interim Maintenance SR Ph+ ALL Arm B (Investigational COG Arm)

4.16.1 Therapy Delivery Map – Capizzi MTX Interim Maintenance SR Ph+ ALL Arm B (Investigational COG Arm) Begin Capizzi MTX Interim Maintenance therapy on Day 64 of Delayed Intensification, or when criteria to start are met. Capizzi MTX Interim Maintenance therapy is 8 weeks (56 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.16.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.16.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
VinCRIStine (VCR)	IV over 1 min*	1.5 mg/m^2/dose **Maximum dose: 2 mg**	1, 11, 21, 31 & 41	*Or infusion via minibag as per institutional policy
Methotrexate (IV MTX)	IV	Start: 100 mg/m^2/dose	1, 11, 21, 31 & 41	As tolerated, escalate subsequent dose by 50 mg/ m^2/dose. Administer IVP or slow bolus (2-15 min). Refer to Section 4.16.3 for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	1 & 31	**Age based dosing.**
Pegaspargase (PEG-ASP)	IV over 1-2 hrs	2500 IU/m^2/dose	2 & 22	Refer to Section 4.16.3 for admin guidelines.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	VCR ____mg	IV MTX ____mg	IT MTX ____mg	PEG-ASP ____IU	Studies
			Enter calculated dose above and actual dose administered below					
		1	____mg ↓	____mg	____mg	____mg		a-e
		2					____IU	
		11		____mg	____mg			c-d
		21		____mg	____mg			c-d
		22					____IU	
		31		____mg	____mg	____mg		c-e
		41		____mg	____mg			c-d
		56						
		57	Begin Maintenance on Day 57 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). If the start of Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.					

See Section 5.0 for Dose Modifications for Toxicities.

4.16.2. Required Observations in Capizzi Methotrexate Interim Maintenance SR Ph+ ALL Arm B (Investigational COG Arm)

a. Physical exam
b. Height, weight
c. CBC with diff/platelets. Collect prior to each MTX dose.
d. Bilirubin, AST, ALT, and creatinine. Collect prior to each MTX dose.
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.16.3 Treatment Details for Capizzi Methotrexate Interim Maintenance SR Ph+ ALL Arm B (Investigational COG Arm)

Begin Capizzi Methotrexate Interim Maintenance when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Vincristine: Intravenous push or infusion via minibag per institutional policy

Days: 1, 11, 21, 31 & 41

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

Methotrexate: Intrathecal
Days: 1 and 31
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Methotrexate: Intravenous push or slow bolus over 2-15 minutes
Day: 1, 11, 21, 31, and 41
Start Dose: 100 mg/m^2/dose
Note: Escalate dose as tolerated; each subsequent dose escalated by 50 mg/m^2/dose. See Section 5.10 for escalation guidelines.

PEG-L-Asparaginase: Intravenously over 1-2 hours
Days: 2 and 22
Dose: 2500 International Units/m^2/dose
PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Capizzi MTX Interim Maintenance, Maintenance starts on Day 57 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3 x upper limit of normal (ULN), AST/ALT ≤ 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.17 Maintenance Cycles 1 –2 SR Ph+ ALL Arm B (Investigational COG Arm)

4.17.1 Therapy Delivery Map –Maintenance Cycles 1- 2 SR Ph+ ALL Arm B (Investigational COG Arm) Begin Maintenance therapy on Day 57 of Capizzi IM or when criteria to start are met. For Cycle 2, begin on Day 85 or when criteria to start are met.	_____ _____ Patient ID number DOB

Treatment details and criteria to start are in Section 4.17.3. Also see 5.9 for details.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.17.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Vincristine (VCR)	IV over 1 min*	1.5 mg/m^2/dose **Maximum dose: 2 mg**	1, 29 & 57	*Or infusion via minibag as per institutional policy
Predniso(LO)ne (PRED)	PO (may be given IV)	20 mg/m^2/dose BID	1-5, 29-33 & 57-61	Total daily dose: 40 mg/ m^2/day, divided BID. Refer to Section 4.17.3. for admin guidelines.
Mercaptopurine (MP)	PO	75 mg/m^2/day	1-84	Refer to Section 4.17.3. & Appendix III for admin guidelines.
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/dose	Once Weekly	Refer to Section 4.17.3. for admin guidelines. Omit when IT MTX is administered.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	1 Also on Day 29 of Cycles 1 - 2 for patients who do NOT receive cranial XRT.	Refer to Section 4.17.3. for admin guidelines. **Age-based dosing.**
For patients with CNS3 disease cranial XRT (See Section 4.17.3. & 16.0) should begin during the first 4 weeks of Maintenance therapy and should be completed by Day 29.				

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib _____mg	VCR _____mg	PRED _____mg _____mg	MP _____mg	PO MTX _____mg	IT MTX _____mg	Studies
			Enter calculated dose above and actual dose administered below						
		1	_____mg	_____mg	_____mg _____mg	_____mg		_____mg	a-e
		5							
		8					_____mg		
		15					_____mg		
		22					_____mg		
		29		_____mg				_____mg	a-e
		33			_____mg _____mg				
		36					_____mg		
		43							
		50					_____mg		
		56					_____mg		a-d
		57		_____mg					
		61			_____mg _____mg				
		64					_____mg		
		71					_____mg		
		78					_____mg		
		84							
		85	Continue to Maintenance Cycle 2 Section 4.18 when criteria to start are met. If the start of continued Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.						

See Section 5.0 for Dose Modifications for Toxicities

4.17.2 Required Observations in Maintenance Cycles 1-2 SR Ph+ ALL Arm B (Investigational COG Arm)

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)
e. CSF cell count, cytospin (with each IT)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.17.3 Treatment Details for Maintenance Cycles 1-2 SR Ph+ ALL Arm B (Investigational COG Arm)

Begin Maintenance therapy on Day 57 after the start of Interim Maintenance #2 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). All oral and intrathecal therapy will be interrupted for myelosuppression as outlined in Section 5.11. Imatinib will be delivered as scheduled, despite myelosuppression.

For supportive therapy each group follows its own guidelines.

The administration schedule below describes one 12-week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

Cranial Radiation Therapy

Patients with CNS3 disease at diagnosis will receive cranial irradiation, 1800cGy in 10 fractions, during the first 4 weeks of Maintenance therapy. Cranial radiation should be completed by Day 29 of Maintenance therapy. See Section 16.0 for details of cranial irradiation.

Dosing should be based on actual BSA.

For supportive guidelines follow own center policy.

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Vincristine: Intravenous push or infusion via minibag per institutional policy

Days: 1, 29 and 57

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

Predniso(LO)ne: Oral (may administer IV)
Days 1-5, 29-33 and 57-67
Dose: 20 mg/m2/dose BID, Total daily dose: 40 mg/ m2/day divided BID
Note: If a patient is unable to take predniSO(LO)NE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 75 mg/m^2/dose
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 525 mg/m^2. See Appendix III for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status.

Methotrexate: Oral
Days: 8, 15, 22, 29*, 36, 43, 50, 57, 64, 71, and 78
Dose: 20 mg/m^2/dose
Note: Day 29 oral MTX is given only to CNS-3 patients receiving cranial radiation. Omit Day 29 oral MTX when IT chemotherapy is given (non-irradiated patients).

Methotrexate: Intrathecal
Day: 1 **(also Day 29 of Cycles 1 and 2, for patients who did NOT receive CNS radiation)**
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

See Section 5.0 for Dose Modifications based on Toxicities.

Following the completion of Maintenance therapy Cycles 1 and 2, continue onto Maintenance therapy Cycle 3 in Section 4.18.

4.18 Maintenance Cycle 3 and Subsequent Cycles SR Ph+ ALL Arm B (Investigational COG Arm)

4.18.1 Therapy Delivery Map –Maintenance Cycle 3 and Subsequent Cycles SR Ph+-ALL Arm B (Investigational COG Arm) Begin Maintenance therapy on Day 85 of the previous Maintenance cycle or when criteria to start are met.	_____ _____ Patient ID number DOB

Treatment details and criteria to start are in Section 4.18.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.18.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Vincristine (VCR)	IV over 1 min*	1.5 mg/m^2/dose **Maximum dose: 2 mg**	1, 29 & 57	*Or infusion via minibag as per institutional policy
Predniso(LO)ne (PRED)	PO	20 mg/m^2/dose BID	1-5, 29-33 & 57-61	Total daily dose: 40 mg/ m^2/day, divided BID. Refer to Section 4.18.3 for admin guidelines.
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/dose	Once weekly	Refer to Section 4.18.3 Omit when IT MTX is administered.
Mercaptopurine (MP)	PO	75 mg/m^2/day	1-84	Refer to Section 4.18.3 & Appendix IV for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	1	Refer to Section 4.18.3 for admin guidelines. **Age-based dosing.**

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	VCR ____mg	PRED ____mg ____mg	PO MTX ____mg	MP ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below						
		1	____mg	____mg	____mg ____mg		____mg	____mg	a-e
		5							
		8				____mg			
		15				____mg			
		22				____mg			
		28							a-d
		29		____mg	____mg ____mg	____mg			
		33							
		36				____mg			
		43				____mg			
		50				____mg			
		56							a-d
		57		____mg	____mg ____mg	____mg			
		61							
		64				____mg			
		71				____mg			
		78				____mg			
		84				____mg			
		85	Continue Maintenance therapy throughout 2 years from the start of protocol therapy, Induction IA. If the start of continued Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.						

See Section 5.0 for Dose Modifications for Toxicities

4.18.2 Required Observations in Maintenance Cycle 3 and Subsequent Cycles SR Ph+ ALL Arm B (Investigational COG Arm)

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.18.3 Treatment Details for Maintenance Cycle 3 and Subsequent Cycles SR Ph+ ALL Arm B (Investigational COG Arm)

Begin Maintenance therapy on Day 85 of the previous Maintenance therapy Cycle. For criteria to start, please follow the dose modifications for low ANC or low platelets (Section 5.11). All oral and intrathecal therapy will be interrupted for myelosuppression as outlined in Section 5.11. Imatinib will be delivered as scheduled, despite myelosuppression.

For supportive therapy each group follows its own guidelines.

The administration schedule describes one 12-week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Vincristine: Intravenous push or infusion via minibag per institutional policy

Days: 1, 29 and 57

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

Predniso(LO)ne: Oral (may administer IV)
Days 1-5, 29-33 and 57-67
Dose: 20 mg/m2/dose BID, Total daily dose: 40 mg/m2/day divided BID
Note: If a patient is unable to take predniSO(LO)NE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 75 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 525 mg/m^2. See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

Methotrexate: Oral
Days: 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78
Dose: 20 mg/m^2/dose

Methotrexate: Intrathecal
Day: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

See Section 5.0 for Dose Modifications based on Toxicities.

Total duration of therapy should be 2 years (104 weeks) from the start of Induction IA therapy.

4.19 Consolidation Block #1 HR Ph+ ALL

4.19.1 Therapy Delivery Map – Consolidation Block #1 HR Ph+ ALL Begin Consolidation therapy after recovery from Induction IB, after risk group and randomized treatment arm assigned, when starting criteria are met. Consolidation Block #1 therapy is 3 weeks (21 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.19.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.19.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal MAH: Methotrexate (IT MTX) Cytarabine (ITARAC) Hydrocortisone (IT HC)	IT	Age (yrs) MTX ARAC HC 1-1.99 8 mg 20mg 8mg 2-2.99 10 mg 26mg 10mg ≥ 3 12 mg 30 mg 12mg	1	Administer ± 6 hours of the start of HDMTX infusion. Refer to Section 4.4.3 for admin guidelines. **Note age-based dosing**
High Dose Methotrexate (HD MTX)	IV over 24 hrs	5000 mg/m^2	1	Refer to Section 4.4.3, Section 5.9.1 & Appendix III for admin guidelines.
Leucovorin (LCV)	PO or IV	15 mg/m^2/dose	3-4	42, 48, and 54 hours after the start of HD MTX infusion. Refer to Section 4.4.3 & Appendix III for admin guidelines. For levoform the dose should be half.
Dexamethasone (DEX)	PO or IV	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day divided BID Refer to Section 4.4.3 for admin guidelines.
Vincristine (VCR)	IV push over 1	1.5 mg/m^2/dose **Maximum dose: 2 mg**	1 & 6	*Or infusion via minibag as per institutional policy.
Cyclophosphamide (CPM)	IV over 30-60 min	200 mg/m^2/dose q12h	2-4	Administer every 12 hours x 5 doses. 1st dose immediately after completion of HDMTX. Refer to Section 4.4.3 for admin guidelines.
High Dose Cytarabine (HD ARAC)	IV over 3 hr	2000 mg/m^2/dose q12h	5	Administer every 12 hours x 2 doses Refer to Section 4.4.3 for admin guidelines.
Pegaspargase (PEG-ASP)	IV over 1-2	2500 IU/ m^2/dose	5	Administer 3 hours following 2nd HD ARAC Refer to Section 4.4.3 for admin guidelines.
Filgrastim (G-CSF) or biosimilar	SubQ	5 mcg/kg/day	7-11	Administer until WBC ≥ 3000/µL. Note additional dosages in comments box in Section 4.4.2. Refer to Section 4.4.3 for admin guidelines.

Continue to the next page for the therapy log.

Therapy Delivery Map – Consolidation Block #1 HR Ph+ ALL

Begin Consolidation therapy after recovery from Induction IB, after risk group and randomized treatment arm assigned, when starting criteria are met. Consolidation Block #1 therapy is 3 weeks (21 days).

_____ Patient ID number

_____ DOB

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	IT: MTX ____mg	ARAC ____mg	HC ___mg	HD MTX ____mg	DEX ____mg	____mg	VCR ____mg	LCV ___mg	CPM ____mg	____mg	HD ARAC ____mg	____mg	PEG-ASP ____IU	Other- ASP ____IU	G-CSF ____mcg	Studies
			Enter calculated dose above and actual dose administered below																
		1	____mg	___mg	___mg	___mg	_ mg	____mg	____mg	____mg									a-e
		2						____mg	____mg				____mg	____mg					
		3						____mg	____mg		____mg		____mg	____mg					
		4						____mg	____mg		____mg ____mg		____mg						
		5						____mg	____mg					____mg	____mg	____IU			
		6								____mg									
		7																____mcg	
		8																____mcg	
		9																____mcg	
		10																____mcg	
		11																____mcg	
		21																	
		22	Continue to Consolidation Block #2 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is at least Grade 1 (whichever occurs later). If the start of Consolidation Block #2 is delared for 2 weeks due to myelosuppression (i.e. if myelosuppression persists 2 weeks after the end of Consolidation Block #1 chemotherapy), imatinib should be held, see Section 5.7.													

See Section 5.0 for Dose Modifications for Toxicities

4.19.1 Required Observations in Consolidation Block #1 HR Ph+ ALL

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.19.2 Treatment Details for Consolidation Block #1 HR Ph+ ALL

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF PROTOCOL THERAPY.

Begin Consolidation Block #1 after risk group classification based on End Induction MRD is finalized and patient has been assigned to **HR Treatment ARM.** The following criteria must be met before starting Consolidation Block #1: ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age and direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT 10x ≤ ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

For supportive therapy follow own center policy

Imatinib: Oral
Days: Daily
Dose: 340 mg/ m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Methotrexate/Cytarabine/Hydrocortisone (MAH): Intrathecal
Days: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	MTX: 8 mg, ARAC 20 mg, HC: 8 mg
2-2.99	MTX: 10 mg, ARAC 26 mg, HC 10 mg
≥ 3	MTX: 12 mg, ARAC 30 mg, HC: 12 mg

Administer ± 6 hours of the start of HDMTX infusion.

High Dose Methotrexate: Intravenous over 24 hours
Day: 1
Dose: 5000 mg/m^2
Note: Administer 500 mg/m^2 over 30 minutes, and the remaining 4500 mg/m^2 over 23.5 hours.

See Section 5.9.1 for hydration, leucovorin rescue and high dose methotrexate infusion guidelines.

Dexamethasone: Oral or Intravenous
Days: 1-5
Dose: 10 mg/m^2/dose **BID,** Total Daily dose: 20 mg/ m^2/dose divided BID

Vincristine: Intravenous push or infusion via minibag per institutional policy
Days: 1 and 6
Dose: 1.5 mg/m^2/dose (maximum dose: 2mg)

Cyclophosphamide: Intravenous over 30-60 mminutes
Days: 2 - 4
Dose: 200 mg/m^2/dose IV
Note: Administer IV every 12 hours x 5 doses, beginning on Day 2. First dose should be given immediately after completion of HD MTX infusion.

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Leucovorin: Oral or Intravenous

Days: 3-4

Dose: 15 mg/m^2/dose x minimum of 3 doses given at 42, 48, and 54 hours after the start of HD MTX infusion. For levoform the dose should be half.

See Section 5.9.1 for hydration, leucovorin rescue and high dose methotrexate infusion guidelines.

High Dose Cytarabine: Intravenous over 3 hours
Day: 5
Dose: 2000 mg/m^2/dose
Note: Administer every 12 hours x 2 doses

Suggested premedications and supportive care: Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2-4 hour schedule.

PEG-L-Asparaginase: Intravenous over 1-2 hours
Day: 5
Dose: 2500 International Units (IU)/m^2/dose
Note: Administer 3 hours after completion of 2nd High Dose Cytarabine.

PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Filgrastim or biosimilar**: Subcutaneous**
Days: 7
Dose: 5mcg/kg/day
Note: Administer daily beginning anytime between Days 7-11 and continue until WBC ≥ 3000/µL. May substitute one-time dose of Peg-filgrastim (100 mcg/kg [maximum 6 mg] x 1 dose) for daily Filgrastim or biosimilar.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Consolidation Block #1, Consolidation Block #2 starts on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.20 Consolidation Block #2 HR Ph+ ALL

4.20.1 Therapy Delivery Map – Consolidation Block #2 HR B-ALL Begin Consolidation therapy on Day 22 of Consolidation Block #1 or when criteria to start are met. Consolidation Block #2 therapy is 3 weeks (21 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.20.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.20.4 for additional details .Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
High Dose Methotrexate (HD MTX)	IV	5000 mg/m^2	1	Refer to Section 4.5.3 & Appendix III for admin guidelines.
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	3-4	42, 48, and 54 hours after the start of HD MTX infusion. Refer to Section 4.5.3 & Appendix III for admin guidelines. For levoform the dose should be half.
Vincristine (VCR)	IV push over 1 min*	1.5 mg/m^2/dose **Maximum dose: 2 mg**	1 & 6	*Or infusion via minibag as per institutional policy Refer to Section 4.5.3 for admin guidelines
Dexamethasone (DEX)	PO or IV	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day divided BID Refer to Section 4.5.3 for admin guidelines.
Intrathecal MAH: Methotrexate (IT MTX) Cytarabine (IT ARAC) Hydrocortisone (IT HC)	IT	Age (yrs) / MTX / ARAC / HC 1-1.99 / 8 mg / 20mg / 8mg 2-2.99 / 10 mg / 26mg / 10mg ≥ 3 / 12 mg / 30 mg / 12mg	1	Administer ± 6 hours of the start of HDMTX infusion. Refer to Section 4.5.3 for admin guidelines. **Note age-based dosing**
Ifosfamide (IFOS)	IV over 1 hr	800 mg/m^2/dose	2-4	1st dose given immediately after HDMTX Q12hr x 5 doses. Refer to Section 4.5.3 for admin guidelines.
Mesna	IV	160 mg m^2/dose	2-4	Administer at hour 0, 4, and 8 from start of each ifosfamide infusion.
Daunorubicin (DAUN)	IV over 1-15 mins	30 mg/m^2/dose	5	Slow IV push of infusion over 1-15 minutes. May be infused over the course of 1 hour. Refer to Section 4.5.3 for admin guidelines.
Pegaspargase (PEG-ASP)	IV over 1-2 hr	2500 IU/m^2/dose	6	Refer to Section 4.5.3 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify: ……	……	……		Refer to Section 4.5.3 for admin guidelines.
Filgrastim (G-CSF) or biosimilar	SubQ	5 mcg/kg/day	7-11	Administer until WBC ≥ 3000/µL. Can use Peg-filgrastim, refer to Section 4.5.3 for admin guidelines

Continue to the next page for the therapy log.

4.20.2 Therapy Delivery Map – Consolidation Block #2 HR Ph+ ALL

Begin Consolidation therapy on Day 22 or when starting criteria is met. Consolidation Block #2 therapy is 3 weeks (21 days).

_____ Patient COG ID number _____ DOB

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ___mg	HD MTX ____mg	VCR ___mg	DEX ___mg ___mg	IT: MTX ARAC HC ___mg ___mg ___mg	IFOS ___mg ___mg	MESNA ____mg	LCV ___mg	DAUN ____mg	PEG-ASP ___IU	Other L-ASP _____ IU	G-CSF ____mcg	Studies
				Enter calculated dose above and actual dose administered below											
		1	____mg	____mg	___mg	___mg ___mg	___mg___mg___mg								a-e
		2				___mg ___mg		___mg ___mg	____mg ____mg ____mg ____mg ____mg ____mg						
		3				___mg ___mg		___mg ___mg	____mg ____mg ____mg ____mg ____mg ____mg	____mg ____mg					
		4				___mg ___mg		___mg	____mg ____mg ____mg	____mg					
		5				___mg ___mg					____mg				
		6			___mg							____IU			
		7												____mcg	
		8												____mcg	
		9												____mcg	
		10												____mcg	
		11												____mcg	
		21													
		22		Continue to Consolidation Block #3 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Continue daily imatinib until Consolidation Block #3 begins. If the start of Consolidation Block #3 is delayed for 2 weeks due to myelosuppression (i.e. if myelosuppression persists 2 weeks after the end of Consolidation Block #2 chemotherapy), imatinib should be held, see Section 5.7.										

See Section 5.0 for Dose Modifications for Toxicities

4.20.3 Required Observations in Consolidation Block #2 HR Ph+ALL

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.20.4 Treatment Details for Consolidation Block #2 HR Ph+ ALL

Begin Consolidation Block #2 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

Dosing should be based on actual BSA. There is a maximum dose of:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

For supportive therapy each group follows its own guidelines.

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Methotrexate/Cytarabine/Hydrocortisone (MAH): Intrathecal
Day: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	MTX: 8 mg, ARAC 20 mg, HC: 8 mg
2-2.99	MTX: 10 mg, ARAC 26 mg, HC 10 mg
≥ 3	MTX: 12 mg, ARAC 30 mg, HC: 12 mg

Give +/- 6 hours from start of HD MTX infusion.

High Dose Methotrexate: Intravenously over 24 hours
Day: 1
Dose: 5000 mg/m^2
Note: Administer 500 mg/ m^2 over 30 minutes, and the remaining 4500 mg/ m^2 over 23.5 hours.

See Section 5.9.1 for HD MTX/LCV rescue and infusion guidelines.

Vincristine: Intravenous push or infusion via minibag per institutional policy

Days: 1 and 6

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

Dexamethasone: Oral or Intravenous
Days: 1-5
Dose: 10 mg/m^2/dose BID, Total Daily dose: 20 mg/ m^2/day divided BID

Ifosfamide: Intravenous over 1 hour
Days: 2-4
Dose: 800 mg/m^2/dose Q12hours x5 doses
Note: Start immediately after the completion of HD MTX infusion.

Suggested hydration: from day 3, if HD MTX is cleared, administer 3,000 mL/m^2/day (125 mL/m^2/hour) using fluid containing D$_5$W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Monitor for adequate urine output as per institution guidelines. May use diuretics (e.g., furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna: Intravenous
Days: 2-4
Dose: 160 mg/m^2/dose
Note: Administer at Hour 0, 4 and 8 from start of each ifosfamide dose.

Leucovorin: Oral or Intravenous
Days: 3-4
Dose: 15 mg/m^2/dose x minimum of 3 doses given at 42, 48, and 54 hours after the start of HD MTX infusion. For levoform the dose should be half.

See Section 5.9.1 for HD MTX/LCV rescue and infusion guidelines.

Daunorubicin: Intravenous over 1-15 minutes
Day: 5
Dose: 30 mg/m^2/dose
Note: May be administered IV push, or over 15-60 minutes per institutional guidelines.

PEG-L-Asparaginase: Intravenous over 1-2 hours
Day: 6
Dose: 2500 International Units/m^2/dose

Note: PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m^2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m^2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase

dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Filgrastim or biosimilar**: Subcutaneous**
Day: 7
Dose: 5mcg/kg/day
Note: Administer daily beginning anytime between Days 7-11 until WBC ≥ 3000/µL. May substitute one-time dose of Peg-filgrastim (100 mcg/kg [maximum 6 mg] x 1 dose) for daily Filgrastim or biosimilar.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Consolidation Block #2, Consolidation Block #3 starts on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.21 Consolidation Block #3 HR Ph+ ALL

4.21.1 Therapy Delivery Map – Consolidation Block #3 HR Ph+ ALL Begin Consolidation Block #3 therapy on Day 22 of Consolidation Block #2 or when criteria to start are met. Consolidation Block #3 herapy is 3 weeks (21 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.21.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.21.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	2000 mg/m^2	1-3	Q 12 hrs x 4 doses Refer to Section 4.6.3 for admin guidelines.
Dexamethasone (DEX)	PO or IV	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day divided BID Refer to Section 4.6.3 for admin guidelines.
Etoposide (ETOP)	IV over 1-2 hrs	100 mg/m^2/dose	3-5	Q 12 hrs x 5 doses Refer to Section 4.6.3 for admin guidelines.
Intrathecal MAH: Methotrexate (IT MTX) Cytarabine (IT ARAC) Hydrocortisone (IT HC)	IT	Age (yrs) / MTX / ARAC / HC 1-1.99 / 8 mg / 20mg / 8mg 2-2.99 / 10 mg / 26mg / 10mg ≥ 3 / 12 mg / 30 mg / 12mg	5	Administer ± 6 hours of the start of HDMTX infusion. Refer to Section 4.6.3 for admin guidelines. **Note age-based dosing**
Pegaspargase (PEG-ASP)	IV over 1-2 hr	2500 IU/ m^2/dose	6	Refer to Section 4.6.3 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify: ……	……..	……	6	Refer to Section 4.6.3 for admin guidelines.
Filgrastim (G-CSF) or biosimilar	SubQ	5 mcg/kg/day	7-11	Administer until WBC ≥ 3000/µL. May use Peg-filgrastim, refer to Section 4.6.3 for admin guidelines

Continue to the next page for the therapy log.

Therapy Delivery Map – Consolidation Block #3 HR Ph+ ALL Begin Consolidation Block #3 therapy on Day 22 of Consolidation Block #2 or when criteria to start are met. Consolidation Block #3 herapy is 3 weeks (21 days).	_____ Patient ID number _____ DOB

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ___mg	HD ARAC ____mg	DEX ___mg ___mg	ETOP ___mg ___mg	IT: MTX ARAC HC ____mg ____mg ____mg	PEG-ASP ___IU	Other L-ASP _____IU	G-CSF ____mcg	Studies
			Enter calculated dose above and actual dose administered below								
		1	____mg	____mg	___mg ___mg						a-d
		2		____mg ____mg	___mg ___mg						
		3		____mg	___mg ___mg	___mg ___mg					
		4			___mg ___mg	___mg ___mg					
		5			___mg ___mg	___mg	___mg ___mg ___mg				e
		6						____mg			
		7								____mcg	
		8								____mcg	
		9								____mcg	
		10								____mcg	
		11								____mcg	
		21									f
		22	Patients with an end of Consolidation MRD ≥ 0.01 go off protocol therapy. HR patients with MRD < 0.01 proceed to HSCT in CR1 after recovery from Consolidation Block #3. Imatinib should be discontinued prior to start of preparative regimen for HSCT. Resume once daily imatinib therapy on Day +56 post-HSCT (Section 4.29) , when **ANC ≥ 750/µL** and **platelets ≥ 75,000/µL** , has Grade I or less acute GVHD, no active/uncontrolled infection, normal organ function (hepatic, and cardiac as defined in Section 4.21.3). HR patients not ready to undergo HSCT (criteria outlined in Section 4.21.3) should continue daily imatinib and continue onto Delayed Intensification (Section 4.22) when peripheral counts recover to **ANC ≥ 500/µL** and **platelets ≥ 50,000/µL** , and creatinine is within normal range for age and direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). If the start of Delayed Intensification #1 is delayed for 2 weeks due to myelosuppression (i.e. if myelosuppression persists 2 weeks after the end of Consolidation Block #3 chemotherapy) imatinib should be held, see Section 5.7.							

See Section 5.0 for Dose Modifications for Toxicities.

4.21.2 Required Observations in Consolidation Block #3 HR Ph+ ALL

a.	Physical Exam
b.	Height, weight
c.	CBC with diff/platelets
d.	Bilirubin, AST, ALT, and creatinine
e.	CSF cell count, cytospin
f.	Bone marrow for MRD assessment by PCR and flow cytometry. Note: *BCR-ABL1* fusion testing by PCR will not be used for MRD determination. Refer to Section 14.1 for sample and shipping details for PCR MRD

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.21.3 Treatment Details for Consolidation Block #3 HR Ph+ ALL

Begin Consolidation Block #3 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

Dosing should be based on actual BSA. There is a maximum dose of:

- **Imatinib, which is capped at a maximum of 800 mg**

For supportive therapy each group follows its own guidelines.

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

High Dose Cytarabine: Intravenous over 3 hours
Day: 1-2
Dose: 2000 mg/m^2/dose
Note: Administer every 12 hours x 4 doses

Suggested premedications and supportive care: Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2-4 hour schedule.

Dexamethasone: Oral or Intravenous
Days: 1-5
Dose: 10 mg/m^2/dose BID, Total Daily dose: 20 mg/ m^2/day divided BID

Etoposide: Intravenous over 1-2 hours
Days: 3-6
Dose: 100 mg/m^2/dose
Note: Administer every 12 hours x 5 doses
The first dose of etoposide should be given approximately 12 hours after the start of the 4th dose of high dose cytarabine.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D_5W Avoid use of large volumes of D_5W due to potential development of hyponatremia. (Recommended concentration: 0,2-0,4 mg/ml).

Methotrexate/Cytarabine/Hydrocortisone (MAH): Intrathecal
Days: 5
Age-based dosing:

Age (yrs)	Dose
1-1.99	MTX: 8 mg, ARAC 20 mg, HC: 8 mg
2-2.99	MTX: 10 mg, ARAC 26 mg, HC 10 mg
≥ 3	MTX: 12 mg, ARAC 30 mg, HC: 12 mg

PEG-L-Asparaginase: Intravenous over 1-2 hours
Day: 6
Dose: 2500 International Units/m^2/dose

Note: PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Filgrastim or biosimilar**: Subcutaneous**
Day: 7
Dose: 5mcg/kg/day
Note: Administer daily beginning anytime between Days 7-11 until WBC ≥ 3000/μL. May substitute one-time dose of Peg-filgrastim (100 mcg/kg [maximum 6 mg] x 1 dose) for daily Filgrastim or biosimilar.

See Section 5.0 for Dose Modifications based on Toxicities.

Required Disease Evaluation
Bone marrow aspirate should be obtained at time of count recovery after completion of Consolidation Block #3. Count recovery is defined as ANC ≥ 500/μL and platelets > 50,000/μL.

Submit bone marrow sample for PCR and flow cytometry MRD testing. Refer to Section 14.1. Note: *BCR-ABL1* fusion testing by PCR will not be used for MRD determination.

Patients with an end of Consolidation Block #3 **MRD ≥ 10^{-2}** go off protocol therapy.

HR patients with end of Consolidation Block #3 **MRD < 10^{-2}** should proceed to HSCT in CR1 as soon as possible after recovery from Consolidation Block #3.

Imatinib should be stopped prior to beginning preparative regimen for HSCT. Resume once daily imatinib therapy on Day +56 post-HSCT (Section 4.29).

HR patients not ready to undergo HSCT immediately after recovery from Consolidation Block #3 for any reason (e.g., suitable donor not yet identified) should continue daily imatinib without interruption. Patients should continue onto Delayed Intensification #1 (Section 4.22) when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age and direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Delayed Intensification #1 may be interrupted at any time to begin HSCT preparative regimen per discretion of the treating clinician. HSCT preparative regimen must start within 21 days of attaining blood count recovery after Delayed Intensification #1.

If time between recovery from Consolidation Block #3 and the start of HSCT preparative regimen is anticipated to be less than 4 weeks, it is allowable for HR patients to receive therapy per HR Interim Maintenance Phase (Section 4.23) instead of proceeding to Delayed Intensification. In this case, HSCT preparative regimen should begin within 4-weeks of starting the Interim Maintenance phase.

4.22 Delayed Intensification #1 HR Ph+ ALL

4.22.1 Therapy Delivery Map – Delayed Intensification #1 Part 1 HR Ph+ ALL Only for HR patients who have not yet proceeded to HSCT, begin DI #1 Part 1 therapy on Day 22 of Consolidation Block #3 or when criteria to start are met. Delayed Intensification therapy is 7 weeks (49 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.22.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.22.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	1	Refer to Section 4.22.4 for admin guidelines. **Note age-based dosing.**
Dexamethasone (DEX)	PO or IV	5 mg/m^2/day BID	1-7 & 15-21	Total daily dose: 10 mg/m^2/day divided BID Refer to Section 4.22.4 for admin guidelines.
Vincristine (VCR)*	IV over 1 min	1.5 mg/m^2/dose **Maximum dose: 2 mg**	8, 15, 22 & 29	*Or infusion via minibag as per institutional policy
DOXOrubicin (DOXO)	IV over 1-15 min	25 mg/m^2/dose	8, 15, 22 & 29	Refer to Section 4.22.4 for admin guidelines. Slow IV push or IV bolus up to 1 hr per institutional guidelines.
Pegasparginase (PEG-ASP)	IV over 1-2	2500 IU/m^2/dose	8	Refer to Section 4.22.4 for admin guidelines.
If PEG-L-Asparaginase at different dose or alternative product specify ……	….....	……	8	Refer to Section 4.7.4 for admin guidelines.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	IT MTX ____mg	DEX ____mg ____mg	VCR ____mg	DOXO ____mg	PEG-ASP ____IU	Other L-ASP _____IU	Studies
				Enter calculated dose above and actual dose administered below						
		1	____mg	____mg	____mg ____mg					a-f
		2			____mg ____mg					
		3			____mg ____mg					
		4			____mg ____mg					
		5			____mg ____mg					
		6			____mg ____mg					
		7			____mg ____mg					
		8				____mg	____mg	____IU		
		14								
		15			____mg ____mg	____mg	____mg			b
		16			____mg ____mg					
		17			____mg ____mg					
		18			____mg ____mg					
		19			____mg ____mg					
		20			____mg ____mg					
		21			____mg ____mg					
		22				____mg	____mg			
		28								
		29				____mg	____mg			
		35		Continue to DI Part 2 (Day 36-49) on the next page. Continue daily imatinib until DI Part 2 begins.						

See Section 5.0 for Dose Modifications for Toxicities.

4.22.2 Therapy Delivery Map – Delayed Intensification #1 Part 2 HR Ph+ ALL Only for HR patients who have not yet proceeded to HSCT. Begin DI Part 2 therapy on Day 36 or when criteria to start are met.	_____ _____ Patient ID number DOB

Delayed Intensification therapy is 7 weeks (49 days). Treatment details and criteria to start are in Section 4.22.4. This Therapy Delivery Map is on **three (3)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	Daily	Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	36	Refer to Section 4.22.4 for admin guidelines.
Thioguanine (TG)	PO	60 mg/m^2/day	36-49	Refer to Section 4.22.4 for admin guidelines.
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose	38-41 & 45-48	Refer to Section 4.22.4 for admin guidelines. Must have ANC ≥ 300/µL and platelets ≥ 30,000/uL to start each 4-day Cytarabine block.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	38 & 45	Refer to Section 4.22.4 for admin guidelines. **Note age-based dosing.**

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	CPM ____mg	TG ____mg	ARAC ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below					
		36	____mg ↓	____mg	____mg ↓		____mg	a-e
		37						
		38				____mg		
		39				____mg		
		40				____mg		
		41				____mg		
		43					____mg	e
		44						
		45				____mg		
		46				____mg		
		47				____mg		
		48				____mg		
		63						
		64	Proceed to HSCT during or immediately after Delayed Intensification #1 as soon as deemed feasible by the treating clinician, If HR patient does not proceed to HSCT after recovery from Delayed Intensification #1, begin Interim Maintenance on Day 64 when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN)), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Continue daily imatinib until Interim Maintenance begins. If the start of Interim Maintenance is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.					

See Section 5.0 for Dose Modifications for Toxicities

4.21.3 Required Observations in Delayed Intensification #1 HR Ph+ ALL

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.21.4 Treatment Details for Delayed Intensification #1 HR Ph+ ALL

HR patients who receive Delayed Intensification #1 therapy should proceed to HSCT during or immediately after recovery from this phase.

This phase is given to HR patients who have not yet proceeded to HSCT. The phase may be interrupted at any time so that patient may proceed to HSCT.

Delayed Intensification #1 is given in 2 parts.

Begin Delayed Intensification #1 Part 1 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Delayed Intensification #1 Part 1 may be interrupted for severe infection and/or major clinical concern. Delayed Intensification #1 may be interrupted at any time to begin HSCT preparative regimen.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Methotrexate: Intrathecal
Day: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Dexamethasone: Oral or Intravenous
Days: 1-7 and 15-21
Dose: 5 mg/m^2/dose BID, Total Daily dose: 10 mg/ m^2/day divided BID

Vincristine: Intravenous push or infusion via minibag per institutional policy
Days: 8, 15, 22 and 29
Dose: 1.5 mg/ m2/dose (maximum dose: 2mg)

Doxorubicin: Slow intravenous push over 1-15 minutes or Intravenous bolus up to 1 hour per institutional guidelines
Days: 8, 15, 22 and 29

Dose: 25 mg/m^2/dose

PEG-L-Asparaginase: Intravenous over 1-2 hours

Day: 8
Dose: 2500 International Units/m^2/dose

Note: PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Criteria to start Delayed Intensification #1 Part 2
Begin Delayed Intensification #1 Pt. 2 on Day 36 or when peripheral counts recover to ANC > 500/µL and platelets > 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3 x upper limit of normal (ULN), AST/ALT < 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Delayed Intensification #1 Part 2 may be interrupted for severe infection and/or major clinical concern. Delayed Intensification #1 Part 2 may be interrupted at any time to begin HSCT preparative regimen.

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

Cyclophosphamide: Intravenous over 30-60 minutes
Day: 36
Dose: 1000 mg/m^2/dose
Note: Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: **Oral**
Days: 36-49
Dose: 60 mg/m2/day
Note: Administer once daily by mouth in the evening on an empty stomach. If taken by tablet, daily doses should be spread as evenly as possible so that the total weekly dose is 420 mg/ m2/day, and the cumulative 14-day dose is 840 mg/ m2/day. See Appendix V for details.

Methotrexate: Intrathecal
Days: 38 and 45
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Cytarabine: Intravenous over 1-30 minutes or subcutaneous
Days: 38-41 and 45-48
Dose: 75 mg/m^2/dose
Note: Must have **ANC ≥ 300/µL** and **platelets ≥ 30,000/uL** to start the 4-day Cytarabine block on Day 43.

See Section 5.0 for Dose Modifications based on Toxicities.

HR patients should proceed to HSCT during or immediately after recovery from Delayed Intensification #1. HSCT preparative regimen should begin within 21 days of attaining blood count recovery after Delayed Intensification #1 phase.

Any HR Ph+ ALL patient who does not proceed to HSCT within 21 days of attaining blood count recovery from Delayed Intensification #1 should continue to receive therapy on the HR chemotherapy backbone plus imatinib until 24 months from the start of Induction IA.

HR patients who do not proceed to HSCT and who were CNS-3 at diagnosis should receive cranial radiation during Interim Maintenance phase (See Section 4.23). All other HR patients who do not proceed to HSCT will be treated without cranial radiation and will receive intrathecal methotrexate during the first 3 cycles of Maintenance as indicated in Section 4.25, 4.26, and 4.27.

For HR patients who are not proceeding to HSCT: The next chemotherapy phase, HR ESPhALL Interim Maintenance, starts at least 14 days from Day 49 of the Delayed Intensification phase or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.23 Interim Maintenance HR Ph+ ALL

4.23.1 Therapy Delivery Map – Interim Maintenance HR Ph+ ALL Only for HR patients who have not yet proceeded to HSCT. Begin Interim Maintenance therapy on Day 64 of DI #1 or when criteria to start are met. Interim Maintenance therapy is 4 weeks (28 days).	_____ _____ Patient ID number DOB

Treatment details and criteria to start are in Section 4.23.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.23.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/ m^2/dose	1, 8, 15, & 22	
Mercaptopurine (MP)	PO	50 mg/ m^2/day	1-28	Refer to Section 4.23.3 & Appendix IV for admin guidelines..
For patients with CNS3 disease cranial XRT (See Section 4.23.3 & 16.0) should begin on Day 1 of Interim Maintenance therapy and should be completed by Day 14.				

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	Studies
			Enter calculated dose above and actual dose administered below			
		1	____mg	____mg	____mg	a-d
		2				
		3				
		4				
		5				
		6				
		7				
		8		____mg		
		15		____mg		
		16				
		17				
		18				
		19				
		20				
		21				
		22		____mg		
		28				
		29	Begin Delayed Intensification #2 on Day 29 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). If the start of Delayed Intensification is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7			

See Section 5.0 for Dose Modifications for Toxicities.

4.23.2 Required Observations in Interim Maintenance HR Ph+ ALL

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.23.3 Treatment Details for Interim Maintenance HR Ph+ ALL

This phase is given to HR patients who have not yet proceeded to HSCT. The phase may be interrupted at any time so that patient may proceed to HSCT.

For HR Ph+ ALL patient not ready to begin HSCT, begin Interim Maintenance on Day 64 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **Imatinib, which is capped at a maximum of 800 mg**

CNS Radiation Therapy (only for HR patients who will definitely not be preceeding to HSCT and who were CNS-3 at diagnosis)

HR Patients who will not be proceeding to HSCT who had CNS3 disease at diagnosis will receive cranial irradiation, 1800cGy in 10 fractions, during the first week of Interim Maintenance therapy, and should be completed within 14 days of starting. See Section 16.0 for details pertaining to cranial irradiation.

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Methotrexate: Oral
Days: 1, 8, 15, and 22
Dose: 20 mg/m^2/dose

Mercaptopurine: Oral
Days: 1-28
Dose: 50 mg/ m^2/day

Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m2 (28-day cumulative dose is 1400 mg/m^2). See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

See Section 5.0 for Dose Modifications based on Toxicities.

Delayed Intensification #2 starts on Day 29 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4.24 Delayed Intensification #2 HR Ph+ ALL

4.24.1 Therapy Delivery Map – Delayed Intensification #2 Part 1 HR Ph+ ALL Only for HR patients who have not yet proceeded to HSCT. Begin DI #2 Part 1 therapy on Day 29 of Interim Maintenance or when criteria to start are met. Delayed Intensification therapy is 7 weeks (49 days).	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.24.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.24.4 for additional details Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	1	Refer to Section 4.24.4 for admin guidelines. **Note age-based dosing.**
Dexamethasone (DEX)	PO or IV	5 mg/m^2/dose BID	1-7 & 15-21	Total daily dose: 10 mg/m^2/day divided BID Refer to Section 4.24.4 for admin guidelines.
Vincristine (VCR)*	IV over 1 min	1.5 mg/m^2/dose **Maximum dose: 2 mg**	8, 15, 22 & 29	*Or infusion via minibag as per institutional policy
Doxorubicin (DOX)	IV over 1-15 min	25 mg/m^2/dose	8, 15, 22 & 29	Slow IV push or IV bolus up to 1 hr per institutional guidelines. Refer to Section 4.24.4 for admin guidelines.
PEG-L_Asparaginase (PEG-ASP)	IV over 1-2 hrs	2500 IU/m^2/dose	8	Refer to Section 4.24.4 for admin guidelines.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Imatinib ____mg	IT MTX ____mg	DEX ____mg ____mg	VCR ____mg	DOXO ____mg	PEG-ASP ____IU	Other L-ASP ____ IU	Studies
			Enter calculated dose above and actual dose administered below							
		1	____mg	____mg	____mg ____mg		____mg			a-e
		2			____mg ____mg					
		3			____mg ____mg					
		4			____mg ____mg					
		5			____mg ____mg					
		6			____mg ____mg					
		7			____mg ____mg					
		8				____mg	____mg	____IU		
		14								
		15			____mg ____mg	____mg	____mg			
		16			____mg ____mg					
		17			____mg ____mg					
		18			____mg ____mg					
		19			____mg ____mg					
		20			____mg ____mg					
		21			____mg ____mg					
		22				____mg	____mg			
		28								
		29				____mg	____mg			
		35		Continue to DI Part 2 (Day 36-49) on the next page.						

See Section 5.0 for Dose Modifications for Toxicities.

4.24.2 Therapy Delivery Map – Delayed Intensification #2 Part 2
HR Ph+ ALL

Only for HR patients who have not yet proceeded to HSCT. Begin DI #2 Pt. 2 therapy on Day 36 or when criteria to start are met. Delayed Intensification therapy is 7 weeks (49 days).

_____ _____
Patient ID number DOB

Treatment details and criteria to start are in Section 4.24.4.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	daily	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/day	36	Refer to Section 4.24.4 for admin guidelines.
Thioguanine (TG)	PO	60 mg/m^2/day	36-49	Refer to Section 4.24.4 for admin guidelines.
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose	38-41 & 45-48	Refer to Section 4.24.4 for admin guidelines. Must have ANC ≥ 300/µL and platelets ≥ 30,000/uL to start each 4-day Cytarabine block
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg ≥ 3 12 mg	38 & 45	Refer to Section 4.24.4 for admin guidelines. **Note age-based dosing.**

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	TG ____mg	CPM ____mg	ARAC ____mg	IT MTX ____mg	Studies
				Enter calculated dose above and actual dose administered below				
		36	____mg	____mg	____mg		____mg	e
		37				____mg		
		38				____mg		
		39				____mg		
		40				____mg		
		41				____mg		
		43					____mg	e
		44						
		45				____mg		
		46				____mg		
		47				____mg		
		48				____mg		
		63						
		64	Begin Maintenance on Day 64 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). If the start of Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.					

See Section 5.0 for Dose Modifications for Toxicities.

4.24.3 Required Observations in Delayed Intensification #2 HR Ph+ ALL

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine
e. CSF cell count, cytospin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.24.4 Treatment Details for Delayed Intensification #2 HR Ph+ ALL

This phase is given to HR patients who have not yet proceeded to HSCT. The phase may be interrupted at any time so that patient may proceed to HSCT.

Delayed Intensification #1 is given in 2 parts.

Begin Delayed Intensification #2 Part 1 on Day 22 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Once Delayed Intensification #2 Part 1 begins, only interrupt for severe infection and/or major clinical concern.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **Vincristine, which is capped at a maximum dose of 2 mg, and**
- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

See Appendix VI for details.

Methotrexate: Intrathecal
Day: 1
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Dexamethasone: Oral or Intravenous
Days: 1-7 and 15-21
Dose: 5 mg/m^2/dose BID, Total Daily dose: 10 mg/m^2/day divided BID

Vincristine: Intravenous push or infusion via minibag per institutional policy
Days: 8, 15, 22 and 29
Dose: 1.5 mg/ m2/dose (maximum dose: 2mg)

Doxorubicin: Slow intravenous push over 1-15 minutes or Intravenous bolus up to 1 hour per institutional guidelines
Days: 8, 15, 22 and 29
Dose: 25 mg/m^2/dose

PEG-L-Asparaginase: Intravenously over 1-2 hours
Day: 8
Dose: 2500 International Units/m^2/dose
PEG-L-Asparaginase can be administered at an inferior dose or can be replaced by native E. Coli L-Asparaginase, according to group policy, iv or im. Native E. Coli L-Asparaginase can be given as a single dose of 25000 IU/m2 in Blocks #1, #2 and #3 and at the dose of 10000 IU/m2 x 4 in two weeks in delayed intensification and Capizzi interim maintenance for each PEG-L-Asparaginase dose. In case of an allergic reaction to the native E. Coli L-Asparaginase, PEG-L-Asparaginase may be used in a single dose for Blocks and delayed intensification or two doses for Capizzi interim maintenance. For patients with history of allergic reaction to PEG-L-Asparaginase, Erwinia L-asparaginase should be administered IM. See Section 5.1 for substitution guidelines.

Delayed Intensification #2 Part 2
Begin Delayed Intensification #2 Pt. 2 on Day 36 or when peripheral counts recover with ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3 x Upper limit of normal (ULN), AST/ALT ≤ 10 x ULN, and mucositis is no worse than Grade 1 (whichever occurs later). Once Delayed Intensification #2 Part 2 begins, interrupt only for severe infection and/or major clinical concern.

Imatinib: Oral
Days: Daily
Dose: 340 mg/m^2/day (maximum dose: 800 mg)

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7)

Cyclophosphamide: Intravenous over 30-60 minutes
Day: 36
Dose: 1000 mg/m^2/dose
Note: Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion

Thioguanine: Oral
Days: 36-49
Dose: 60 mg/m^2/day
Note: Administer once daily by mouth in the evening on an empty stomach. If taken by tablet, daily doses should be spread as evenly as possible so that the total weekly dose is 420 mg/ m^2/day, and the cumulative 14-day dose is 840 mg/ m^2/day. See Appendix V for details.

Methotrexate: Intrathecal
Days: 38 and 45
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Cytarabine: Intravenously over 1-30 minutes or Subcutaneous
Days: 38-41 and 45-48
Dose: 75 mg/m^2/dose
Note: Must have **ANC ≥ 300/µL** and **platelets ≥ 30,000/µL** to start the 4-day Cytarabine block on Day 43.

See Section 5.0 for Dose Modifications based on Toxicities.

Begin Maintenance on Day 50 or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, creatinine is within normal range for age, direct bilirubin ≤ 3x upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is no worse than Grade 1 (whichever occurs later).

4. 25 Maintenance Cycle 1 HR Ph+ ALL

4.25.1 Therapy Delivery Map –Maintenance Cycle 1 HR Ph+ ALL Only for HR patients who have not proceeded to HSCT. Begin Maintenance therapy on Day 50 of DI or when criteria to start are met.	_____ Patient ID number _____ DOB

Extensive details and criteria to start are in Section 4.25.3 (treatment overview).

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.25.3 for additional details Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/dose	Once weekly	Refer to Section 4.25.3
Mercaptopurine (MP)	PO	50 mg/m^2/day	1-84	Refer to Section 4.25.3 & Appendix IV for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 MTX 8 mg 2-2.99 MTX 10 mg ≥ 3 MTX 12 mg	1 & 43	Note: Administer once every 6 weeks, 6 total doses. Discontinue after 6th dose. Only administer to non-irradiated patients. Refer to Section 4.25.3 for admin guidelines.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below				
		1	____mg	____mg	____mg	____mg	a-e
		8		____mg			
		15		____mg			
		22		____mg			
		29		____mg			a-d
		36		____mg			
		43		____mg		____mg	e
		50		____mg			
		57		____mg			a-d
		64		____mg			
		71		____mg			
		78		____mg			
		84					a-d
		85	Continue Maintenance therapy Cycle 2 in Section 4.26. If continued Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.				

See Section 5.0 for Dose Modifications for Toxicities.

4.24.2 Required Observations in Maintenance Cycle 1 HR Ph+ALL

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)
e. CSF cell count, cytospin with each IT; ^collect 6 samples in total.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.25.3 Treatment Details for Maintenance Cycle 1 HR Ph+ ALL

Begin Maintenance therapy on Day 50 of Delayed Intensification or when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL, and creatinine is within normal range for age, direct bilirubin ≤ 3x Upper limit of normal (ULN), AST/ALT ≤ 10x ULN, and mucositis is at least Grade 1 (whichever occurs later). For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). Oral and intrathecal therapy will be interrupted for myelosuppression as outlined in Section 5.11. Imatinib will be delivered as scheduled, despite myelosuppression.

The administration schedule describes the 12-week cycle of Maintenance therapy Cycle 1.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 50 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m^2. See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

Methotrexate: Oral
Days: 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78
Dose: 20 mg/m^2/dose

Methotrexate: Intrathecal
Day: 1 & 43
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

See Section 5.0 for Dose Modifications based on Toxicities.

Following the completion of Maintenance therapy Cycle 1, continue onto Maintenance therapy Cycle 2 in Section 4.26.

4.26 Maintenance Cycle 2 HR Ph+ ALL

4.26.1 Therapy Delivery Map –Maintenance Cycle 2 HR Ph+ ALL Only for HR patients who have not proceeded to HSCT. Begin Maintenance Cycle 2 therapy on Day 85 of Maintenance therapy Cycle 1 or when criteria to start are met.	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.26.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.26.3 for additional details Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/dose	Once weekly	Refer to Section 4.26.3
Mercaptopurine (MP)	PO	50 mg/m^2/day	1-84	Refer to Section 4.26.3 & Appendix IV for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 MTX 8 mg 2-2.99 MTX 10 mg ≥ 3 MTX 12 mg	1 & 43	Note: Administer once every 6 weeks, 6 total doses. Discontinue after 6th dose. Only administer to non-irradiated patients. Refer to Section 4.26.3 for admin guidelines.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below				
		1	____mg	____mg	____mg	____mg	a-e
		8		____mg			
		15		____mg			
		22		____mg			
		29		____mg			a-d
		36		____mg			
		43		____mg		____mg	e
		50		____mg			
		57		____mg			a-d
		64		____mg			
		71		____mg			
		78		____mg			
		84					
		85	Continue Maintenance therapy Cycle 3 in Section in 4.27. If continued Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.				

See Section 5.0 for Dose Modifications for Toxicities.

4.26.2 Required Observations in Maintenance Cycle 2 HR Ph+ ALL

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)
e. CSF cell count, cytospin with each IT; ^collect 6 samples in total.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.26.3 Treatment Details for Maintenance Cycle 2 HR Ph+ ALL

Continue onto Maintenance therapy Cycle 2 on Day 85 of the previous Maintenance cycle. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). Oral and intrathecal therapy will be interrupted for myelosuppression as outlined in Section 5.11. Imatinib will be delivered as scheduled, despite myelosuppression.

The administration schedule describes the 12-week cycle of Maintenance therapy Cycle 2.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg dose.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 50 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m^2. See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

Methotrexate: Oral
Days: 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78
Dose: 20 mg/m^2/dose

Methotrexate: Intrathecal
Day: 1 & 43
Note: Administer once every 6 weeks, 6 total doses. Discontinue after 6th dose.
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Note: IT MTX is not given during Maintenance in CNS3 patients who received cranial radiation.

See Section 5.0 for Dose Modifications based on Toxicities.

Following the completion of Maintenance Therapy Cycle 2, continue onto Maintenance Therapy Cycle 3 in Section 4.27.

4.27 Maintenance Cycle 3 HR Ph+ ALL

4.27.1 Therapy Delivery Map –Maintenance Cycle 3 HR Ph+ ALL Only for HR patients who have not proceeded to HSCT. Begin Maintenance Cycle 3 therapy on Day 85 of Maintenance therapy Cycle 2 or when criteria to start are met.	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.27.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.27.3 for additional details Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/dose	Once weekly	Refer to Section 4.27.3
Mercaptopurine (MP)	PO	50 mg/m^2/day	1-84	Refer to Section 4.27.3 & Appendix IV for admin guidelines.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 MTX 8 mg 2-2.99 MTX 10 mg ≥ 3 MTX 12 mg	1 & 43	Administer once every 6 weeks, 6 total doses. Discontinue after 6th dose. Only administer to non-irradiated patients. Refer to Section 4.27.3 for admin guidelines.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	IT MTX ____mg	Studies
			Enter calculated dose above and actual dose administered below				
		1	____mg	____mg	____mg	____mg	a-e
		8		____mg			
		15		____mg			
		22		____mg			
		29		____mg			a-d
		36		____mg			
		43		____mg		____mg	e
		50		____mg			
		57		____mg			a-d
		64		____mg			
		71		____mg			
		78		____mg			
		84					
		85	Continue Maintenance therapy Cycle 4 in Section 4.28. If continued Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.				

See Section 5.0 for Dose Modifications for Toxicities.

4.27.2 Required Observations in Maintenance Cycle 3 HR Ph+ ALL

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)
e. CSF cell count, cytospin with each IT

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.27.3 Treatment Details for Maintenance Cycle 3 HR Ph+ ALL

Begin Maintenance therapy Cycle 3 on Day 85 of the previous Maintenance cycle. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). Oral and intrathecal therapy will be interrupted for myelosuppression as outlined in Section 5.11. Imatinib will be delivered as scheduled, despite myelosuppression.

The administration schedule describes the 12-week cycle of Maintenance therapy Cycle 3.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is no maximum dosing, except for:
Imatinib, which is capped at a maximum of 800 mg

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg dose.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 50 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m^2. See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

Methotrexate: Oral
Days: 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78
Dose: 20 mg/m^2/dose

Methotrexate: Intrathecal
Day: 1 & 43
Age-based dosing:

Age (yrs)	Dose
1-1.99	8 mg
2-2.99	10 mg
≥ 3	12 mg

Note: IT MTX is not given during Maintenance in CNS3 patients who received cranial radiation.

See Section 5.0 for Dose Modifications based on Toxicities.

Following the completion of Maintenance Therapy Cycle 3, continue onto Maintenance Therapy Cycle 4 in Section 4.28.

4.28 Maintenance Cycle 4 and Subsequent Cycles HR Ph+ ALL

4.28.1 Therapy Delivery Map –Maintenance Cycle 4 and Subsequent Cycles HR Ph+ ALL Only for HR patients who have not proceeded to HSCT. Begin Maintenance therapy on Day 85 of the previous Maintenance cycle or when criteria to start are met.	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.28.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.28.3 for additional details Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Oral Methotrexate (PO MTX)	PO	20 mg/m^2/dose	Once weekly	Refer to Section 4.28.3
Mercaptopurine (MP)	PO	50 mg/m^2/day	1-84	Refer to Section 4.28.3 & Appendix IV for admin guidelines.

Enter Cycle #: _____ **Ht _____cm** **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib ____mg	PO MTX ____mg	MP ____mg	Studies
			Enter calculated dose above and actual dose administered below			
		1	____mg	____mg	____mg	a-d
		8		____mg		
		15		____mg		
		22		____mg		
		29		____mg		a-d
		36		____mg		
		43		____mg		
		50		____mg		
		57		____mg		a-d
		64		____mg		
		71		____mg		
		78		____mg		
		84				
		85	Total duration of therapy should be 2 years from the start of protocol therapy, Induction IA. If continued Maintenance therapy is delayed for 2 weeks due to myelosuppression, imatinib should be held, see Section 5.7.			

See Section 5.0 for Dose Modifications for Toxicities.

4.28.2 Required Observations in Maintenance Cycle 4 and Subsequent Cycles HR Ph+ALL

a. Physical exam (every 4 weeks)
b. Height, weight (every 4 weeks)
c. CBC with diff/platelets (every 4 weeks)
d. Bilirubin and AST/ALT (every 4 weeks)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.28.3 Treatment Details for Maintenance Cycle 4 and Subsequent Cycles HR Ph+ ALL

Begin Maintenance therapy on Day 85 of the previous Maintenance cycle. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.11). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.11. Imatinib will be delivered as scheduled, despite myelosuppression.

Maintenance consist of 12-week cycles repeated until total duration of therapy is 2 years from the start of Induction IA therapy.

The administration schedule describes one 12-week cycle of Maintenance therapy.

For supportive therapy each group follows its own guidelines.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **Imatinib, which is capped at a maximum of 800 mg**

Imatinib: Oral
Days: Daily until completion of treatment
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg dose.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Mercaptopurine: Oral
Days: Daily until completion of treatment
Dose: 50 mg/m^2/day
Note: If taken by tablet, daily doses should be spread as evenly as possible so that total weekly dose is 350 mg/m^2. See Appendix IV for details.

It is strongly recommended that mercaptopurine be taken at the same time each day.

Methotrexate: Oral
Days: 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78
Dose: 20 mg/m^2/dose

See Section 5.0 for Dose Modifications based on Toxicities.

Total duration of therapy should be 2 years (104 weeks) from the start of Induction IA therapy.

4.29 Imatinib Therapy Post-HSCT HR Ph+ ALL

4.29.1 Imatinib Therapy Post-HSCT HR Ph+ ALL	
Begin imatinib therapy on Day +56 post-HSCT when **ANC ≥ 750/µL** and **platelets ≥ 75,000/µL**, patient has Grade 1 or less acute GvHD, no active/uncontrolled infection, total direct bilirubin ≤ 2.0 mg/dL, and normal cardiac function defined as: a shortening fraction of ≥ 27% by echocardiogram, or ejection fraction of ≥ 50% by echocardiogram or by radionuclide angiogram, and corrected QT Interval, QTc < 480mSec. Continue post-HSCT through Day +365.	_____ Patient ID number _____ DOB

Treatment details and criteria to start are in Section 4.29.3.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, divided twice daily. See Section 4.29.3 for additional details Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	Imatinib _____mg	Studies
			Enter calculated dose above and actual dose administered below	
		+56/1	_____mg	a-c
		84	_____mg	
		90	_____mg	
		112	_____mg	
		140	_____mg	
		168	_____mg	
		180	_____mg	c
		196	_____mg	
		224	_____mg	
		252	_____mg	
		280	_____mg	
		308	_____mg	
		336	_____mg	
		365	_____mg	c--f

See Section 5.0 for Dose Modifications for Toxicities.

4.29.2 Required Observations Imatinib Therapy Post-HSCT HR Ph+ ALL

a.	CBC with diff/platelets on Day +56
b.	Bilirubin and AST/ALT on Day +56
c.	For patients who consent submit a bone marrow sample on Day +56 (Day 1 of post-HSCT) and +180 (6 months) and +365, for MRD testing. Refer to section 14.2.
d.	Physical exam on Day +365
e.	Height, weight on Day +365
f.	MUGA or ECHO on Day +365

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

4.29.3 Treatment Details for Imatinib Therapy Post-HSCT HR Ph+ ALL

Begin imatinib therapy on Day +56 of post-Hematopoietic Stem Cell Therapy (HSCT), when **ANC ≥ 750/µL** and **platelets ≥ 75,000/µL**, patient has Grade 1 or less acute GvHD, no active/uncontrolled infection, total direct bilirubin ≤ 2.0 mg/dL, and normal cardiac function is defined as, a shortening fraction of ≥ 27% by echocardiogram, or ejection fraction of ≥ 50% by echocardiogram or by radionuclide angiogram, and corrected QT Interval, QTc < 480mSec. Imatinib therapy post-HSCT continues throughout Day +365.

The administration schedule describes Day +56 through Day +365 of imatinib therapy post-HSCT.

Dosing should be based on actual BSA. There is a maximum dose for: Imatinib, which is capped at a maximum of 800 mg

Imatinib: Oral
Days: Daily until Day +366 post-HSCT (i.e., last dose on Day +365 post-HSCT).
Dose: 340 mg/m^2/day (maximum dose: 800 mg)
Note: Administer doses > 600 mg/ day divided twice daily

The imatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary. For those taking tablets, dose may be rounded to the nearest 50 mg dose.

Imatinib should be given daily throughout phase without interruption. Hold only for toxicity (Section 5.7).

See Appendix VI for details.

Research Studies
For patients who consent submit bone marrow samples for MRD testing. Refer to Section 14.2 for details.

See Section 5.0 for Dose Modifications based on Toxicities.

Post-HSCT imatinib therapy is completed after the dose administered on Day +365.

5 DOSE MODIFICATIONS FOR TOXICITIES

Notify the Study Chair at the time of removing a patient from protocol therapy for toxicity. The drugs are listed in alphabetical order.

5.1 Asparaginase (PEG-L-Asparaginase or Erwinia L-Asparaginase)

Allergy

Local Allergic Reactions (inflammation at injection site, swelling): Note these recommendations only apply when the asparaginase product is administered intramuscularly. Continue asparaginase administration in the presence of Grade 1 allergy as defined by CTCAE v4.0 (transient flushing or rash; drug fever < 38ºC).

Systemic Allergic Reactions: In the event of Grade 1 reactions, characterized by transient flushing or rash and drug fever < 38ºC, without the need for treatment with antihistamines or steroids, the dose of asparaginase being administered intravenously may be continued with close observation.

Discontinuation is recommended for Grade 2 or higher allergic reactions as defined by CTCAE v4.0, which require medical intervention.

Note: Premedication with antihistamines and/or corticosteroids to decrease the risk of overt allergy symptoms may mask the appearance of systemic allergy and should be used with caution. If premedication is used, it may be prudent to monitor asparaginase activity following the dose. 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, PEG-L-Asparaginase can be substituted for native E.Coli L-Asp or Erwinia L-asparaginase for PEG-L-Asparaginase.

Anaphylaxis

Discontinue pegaspargase if the patient develops Grade 3 anaphylaxis as defined by CTCAE v4.0 (symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; allergy-related edema/angioedema; hypotension). If this occurs, *Erwinia* asparaginase should be substituted.

COG AALL07P2 showed that Erwinia L-asparaginase was well tolerated and achieved nadir serum asparaginase activity at both 48 and 72 hours after dosing that was similar to that achieved with pegaspargase. Based on these and other data, the FDA initially approved *Erwinia* asparaginase for use following allergy to pegaspargase, with a dose of Erwinia 25,000 IU/m^2 x 6 doses IM on a Monday/Wednesday/Friday schedule substituted for a single dose of pegaspargase. In December 2014, the FDA expanded its approval to include intravenous as well as intramuscular administration. However, in a trial of IV *Erwinia*, serum asparaginase activity level of 0.01 IU/mL was observed in 83 % of patients 48 hours after a dose, but in only 43% (mean ± SD; 0.32 IU/ml ± 0.23), and in 43% of patients 72 hour post-dose. Thus, if Erwinia asparaginase is administered IV, the recommended dosing is every 48 hours rather than on a Monday/Wednesday/Friday schedule.

For allergic reaction native E. Coli L-Asparaginase could be replaced by a single dose of PEG-L-Asparaginase for Blocks #1,#2 and #3 and Delayed intensification and 2 doses for Capizzi interim maintenance. For substitution of PEG-L-Asparaginase with Erwinia L-asparaginase use the following schedule:

Phase(s) of Treatment	**Drug(s)**	**Replacement Schedule for Erwinia asparaginase**
Consolidation Blocks#1,#2 and #3, Interim Maintenance, Delayed Intensification	One or more doses of Peg-L-asparaginase (2,500 IU/m^2)	25,000 IU/m^2/dose IM M/W/F x 6 doses for each dose of pegaspargase 25,000 IU/m2/dose IV q 48 hours x 7 doses for each dose of PEG-L-Asparaginase

To replace a dose of intravenous PEG-L-Asparaginase that was discontinued during the infusion due to an allergic reaction, the following recommendations may be used to guide patient care.

In the event that a PEG-L-Asparaginase infusion is discontinued for an allergic reaction, regardless of amount received, substitution with *Erwinia* asparaginase should begin approximately 48 hours after pegaspargase has been discontinued and preferably to coincide with the Monday/Wednesday/Friday administration schedule detailed above in patients who are clinically stable. Up to 6 doses of IM *Erwinia* asparaginase (or 7 doses of IV *Erwinia*) 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.

Silent Inactivation: Therapeutic Drug Monitoring (TDM) of asparaginase activity can be performed. Centers may elect to discontinue native E. Coli L-Asparaginase or PEG-L-Asparaginase 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.

Coagulopathy: If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor VIIa). Each group folllows its own guidelines for coagulopathy.

Hyperbilirubinemia: Asparaginase may need to be withheld in patients with an elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity. Asparaginase should be withheld in patients with direct bilirubin > 2.0 mg/dL. Dose may be administered without dose-reduction if direct bilirubin falls to $\leq$ 2.0 mg/dL within 7 days of the day that the dose was initially due; if hyperbilirubinemia persists beyond that time, dose should be omitted and not made up.

Hyperglycemia: Do not modify dose. Treat hyperglycemia as medically indicated.

Hyperlipidemia: Do not modify dose.

Ketoacidosis: Hold asparaginase until blood glucose can be regulated with insulin.

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 or 4 pancreatitis is a contraindication to additional asparaginase administration.

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, which is not catheter-related, consider evaluation for inherited predisposition to thrombosis.

CNS Events (bleed, thrombosis or infarction): Hold asparaginase. Treat with FFP, factors or anticoagulation as appropriate. Consider resuming 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.

5.2 Cyclophosphamide

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/m^2/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.

Renal Dysfunction: If creatinine clearance or radioisotope GFR is < 10 mL/min/1.7 m^2, reduce dose of cyclophosphamide by 50%. Prior to dose adjustment of cyclophosphamide, the creatinine clearance should be repeated with good hydration.

5.3 Cytarabine (ARAC)

ARAC Syndrome: Do not withhold cytarabine for fever if it is likely to have been caused by the cytarabine. Obtain blood cultures if a central line is present. For rash or conjunctivitis, withhold for Grade 3-4 toxicity until resolved. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis. Once Induction IB or Delayed Intensification (DI) has started do not interrupt for uncomplicated myelosuppression; interrupt only for severe infection and/or major clinical concern. Do make up missed doses.

Adequate renal function (defined as creatinine within normal range) is required for the administration of high dose cytarabine. Creatinine Clearance should be measured for

patients with elevated creatinine or suspected renal insufficiency. For CrCl < 60 mL/min/1.73 m^2, hold pending recovery and omit if recovery requires > 3 weeks.

5.4 Daunorubicin and Doxorubicin (Anthracyclines)

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 4.0.

Note: use the following updated term to report decreases in the EF or SF: *cardiac disorders-others*.

Myelosuppression (beyond Induction): If patient has severe infection or severe mucositis (Grade 3-4) and an ANC < 500/μL delay anthracycline during phases other than Induction IA. During Induction IA, continue with anthracycline administration. Subsequent doses should be given at full dose.

Hyperbilirubinemia:[35]

Direct Bili	% Dose Reduction
> 2.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

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 group or institutional guidelines.

5.5 Etoposide (VP-16)

Infusion modality: Etoposide can be mixed in 0.9% NaCl or D_5W Avoid use of large volumes of D_5W due to potential development of hyponatremia. (Recommended concentration: 0.2-0.4 mg/ml).

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), which is statistically indistinguishable from that measured for etoposide at equimolar doses.

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.

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%.

Hyperbilirubinemia: If direct bilirubin is > 2 mg/dL, hold etoposide.

5.6 Ifosfamide

Microscopic Hematuria: For transient microscopic hematuria (no more than 2 abnormal urinalyses on 2 separate days during a cycle of therapy), there is no modification of the ifosfamide or MESNA.

For persistent microscopic hematuria (> 2 abnormal urinalyses during a cycle of therapy), increase hydration to 3500-4000 mL/m^2/day and daily MESNA dose to 100% of the ifosfamide dose.

Gross Hematuria: All episodes of gross hematuria should be evaluated in conjunction with pediatric surgical or urologic consult. Further testing, such as cystoscopy, urine culture, excretory urogram, and voiding cystogram should also be considered and performed as indicated.

For transient gross hematuria (only 1 episode, which clears to less than gross hematuria) during the cycle of therapy, do not modify the ifosfamide dose. Use continuous infusion MESNA, as below.

For persistent gross hematuria occurring during the ifosfamide cycle, withhold further ifosfamide.

Continuous Infusion MESNA Regimen: Give MESNA at 20% of the ifosfamide dose, mixed with the ifosfamide, and then give MESNA at 10% of the ifosfamide dose per hour for 24 hours by continuous IV infusion.

Acute Neurotoxicity: This is an organic brain syndrome that ranges from mild confusion and disorientation to seizures, ataxia, and coma. It may be aggravated by impaired renal function. It usually, but does not always, resolve spontaneously, and it may or may not recur with subsequent doses. If symptoms are mild and transient cycle may continue with strict avoidance of potentially aggravating co-administered medications such as sedatives and anticholinergic drugs. If Grade 4 neurotoxicity occurs during ifosfamide administration, investigators may consider administration of methylene blue at 2 mg/kg [Maximum dose: 50 mg] on the day this occurs. The methylene blue dose may be repeated at 4 hours and 8 hours after ifosfamide administration, following which ifosfamide should be discontinued and no further ifosfamide will be administered.
Hypersensitivity, renal impairment and glucose-6-phosphate dehydrogenase (G-6PD) deficiency are contraindications to the administration of methylene blue.

5.7 Imatinib

Hematologic:

A. During Chemotherapy (all SR patients and HR patients prior to HSCT):

Do not hold or reduce dose for low blood counts, unless prolonged (resulting in a > 14 day delay in next block of chemotherapy).

Prior to Maintenance: If neutropenia and/or thrombocytopenia results in delay of next block of chemotherapy by > 14 days: Hold imatinib and resume at the same dose once ANC/platelet counts recover sufficiently to begin the next block of treatment. If subsequent blocks of treatment are delayed for >14 days due to neutropenia and/or thrombocytopenia, imatinib should be held, and dose may be reduced when restarted after ANC/platelet count recovery (e.g., 20% dose reduction of imatinib).

During Maintenance: If ANC falls below 500/μL or if platelet count falls below 50,000/μL: continue imatinib but hold 6MP and methotrexate, as indicated below. If after 2 weeks of holding methotrexate/6MP, ANC remains below 500/μL or platelet count below 50,000/μL, imatinib should be held. Imatinib should be restarted without dose reduction once counts recover (ANC ≥ 500/μL, platelets ≥ 50,000 μL).

For recurrent neutropenia/thrombocytopenia: First reduce doses of 6MP/methotrexate, as indicated below. Imatinib dose may be reduced by 20% if low blood counts recur in patients already receiving dose-reduced 6MP/methotrexate.

B. Post-HSCT (HR patients):
If ANC falls below 500/μL or if platelet count falls below 50,000/μL: hold imatinib. Re-check counts at least weekly. Restart imatinib at full dose once counts recover (ANC ≥ 500/μL, platelets ≥ 50,000 μL).

For recurrent neutropenia/thrombocytopenia: Hold imatinib. Reduce dose by 20% when counts recover (ANC ≥ 500/μL, platelets ≥ 50,000 μL).

Hepatic:

A. Direct Bilirubin elevation:
Hold imatinib for direct bilirubin > 2.0 mg/dL. Restart when direct bilirubin is Grade 1 or lower (< 1.5 x ULN). Resume at full dose. Reduce dose by 20% if elevation of direct bilirubin recurs.

B. Elevated AST/ALT:
Hold imatinib for ALT/SGPT or AST/SGOT > 20x ULN (Grade 4). Restart at full dose when AST/ALT < 5x ULN (Grade 2 or less). If liver dysfunction recurs, reduce dose of imatinib by 20% only after dose reducing other chemotherapy (eg, MTX/6MP during maintenance) and withholding other potentially causative agents.

Infection: Hold imatinib for Grade 4 infection until clinically improved (Grade 3 or lower), and then restart without dose reduction. Do not hold for uncomplicated less severe infections (Grade 3 or lower).

Cardiac Toxicity: For Grade 1 QTc elevation: hold other agents associated with prolonged QTc. If no improvement, then imatinib should be held until resolution, and then restarted. For Grade 2 or higher QTc interval, hold imatinib. Imatinib may be resumed once QTc prolongation resolves (< Grade 1). Imatinib dose may be reduced by 20% if QTc prolongation recurs.

Edema/Effusions: If the patient experiences Grade 3 or higher pericardial, pleural effusions, or edema, hold imatinib. Resume full-dose imatinib when edema/effusion resolves if thought to be unrelated or unlikely to be related to imatinib. If the effusion is felt to be caused by imatinib, then consider restarting imatinib at 80% dose when resolved. Close follow-up is warranted after restarting imatinib in the latter situation.

Other Grade 3 or higher Non-Hematologic Toxicity: Holding imatinib or reducing dose is discouraged. However, if patient experiences Grade 3 or higher non-hematologic toxicity that is thought to be likely or definitely related to imatinib that does not resolve despite symptomatic treatment, imatinib may be held after discussion with Principal Investigator or designee. In such instances, imatinib should be restarted once toxicity has resolved to Grade 2 or lower.

5.8 Intrathecal Methotrexate/MAH Intrathecal Therapy

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/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC < 500/μL) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

Dose modifications following an episode of acute neurotoxicity:
Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.[36-38] 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.[38-43] It is clear however, that CNS prophylaxis is a mandatory component of curative therapy for children with ALL.

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.[44] MRI abnormalities may be pronounced, but transient. Posterior reversible encephalopathy may be present on MR with extensive diffusion abnormalities, but these do not appear to correlate with subsequent demyelination or gliosis.[45-47] 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.[48] 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 ARAC for 1 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 12 hours x 2 doses beginning 48 hours after the LP. This pattern of rescue was associated with a clear diminution in the incidence of acute neurotoxicity in one case series.[48] 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 48 hours later would minimize any potential interference. If the event does not recur, resumption of standard therapy should be considered, following 1 modified or omitted IT dose. In the face of 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 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.[49-52] Dramatic deviations from protocol recommended therapy might result in the child being taken off 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.[53-56] At doses thought to be therapeutic, side effects have included nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. In addition, Hollander et al [57] 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.

<u>Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture</u>:

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.

Viral, bacterial, or fungal meningitis: Omit until resolved.

5.9 High-Dose Methotrexate (HDMTX) and Leucovorin Rescue

[*Please note that **HDMTX** refers to* IV *MTX **5000 mg/m^2 given over 24** **hrs***]
Review of methotrexate dosing on BFM-based protocols indicated that excessive methotrexate toxicity has not been encountered in patients larger than 2 m^2 who receive more than 10 grams of methotrexate. The investigator should base the methotrexate on the patient's meter-squared dosing and not cap at 10 grams of methotrexate.

HD MTX Infusion Guidelines. The following guidelines or national ones can be followed.

See Appendix III for a flowchart of the HDMTX / LCV guidelines.

When IT therapy and HDMTX are scheduled for the same day, 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 TMP-SMX on the days of HDMTX infusion and for at least 72 hours after the start of the HDMTX infusion and until the MTX level is less than 0.4 µM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 µM.*

Hold any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HDMTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 µM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 µM.*

Recommended Prehydration with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. 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 and pH at above parameters. An acetate or bicarbonate bolus (0.5 mEq/kg 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 HDMTX infusion and until MTX has cleared. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below < 0.1µM [levels specified by the protocol].

Hour 0: MTX 500 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the HDMTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Hours 24, (36), 42 and 48: Draw MTX level and serum creatinine; NOTE: 36 hour level is only drawn if needed (see below)

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, assure appropriate urine pH and urine volume as above and draw a 42 hour level. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (see below). For patients with delayed clearance during a previous course, begin the following course with the increased hydration (200 mL/m^2/hr). If subsequent course is not associated with delayed clearance, attempt to use standard hydration.

If the 24 hour level is < 150 μM draw the next level at hour 42 and refer to table below.

If the 24 hour level is ≥ 150 μM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to the table below.

If the 42 and 48 hour levels are ≤ 1 and 0.4 μM, respectively, give Leucovorin at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin.

(36 hr MTX level)	42 hr MTX level	48 hr MTX level	Leucovorin Rescue++
Only required if 24 hr level is ≥ 150 μM. See below for guidelines**	1.01 to 9.9 μM	0.41 to 5.9 μM	Continue 15 mg/m^2 q 6h until MTX level < 0.1 μM (draw q12-24 h).
	10 to 19.9 μM	6 to 9.9 μM	Increase to 15 mg/m^2 q 3h until MTX level < 0.1 μM (draw q 6-24 h). Consider glucarpidase.
	20 to 200 μM	10 to 100 μM	Increase to 100 mg/m^2 q 6h until MTX level < 0.1 μM (draw q 6-24 h). Consider glucarpidase.
	> 200 μM	> 100 μM	Increase to 1000 mg/m^2 q 6h until MTX level < 0.1 μM (draw q 6-24 h). Consider glucarpidase.

** **If the 36 hour level exceeds 3 μM**, 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 urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also **consider glucarpidase if 36 hour MTX level exceeds 10 μM** (see below).

++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤ 1 and/or ≤ 0.4 μM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

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 renal function does not

recover, omit MTX. Do not give HDMTX 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 G_2, Voraxaze™).[58,59]

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 MTX
< 10x ULN	Continue with therapy as scheduled
10 – 20x ULN	Continue with therapy as scheduled for 1 cycle
10 – 20x ULN for 2 consecutive cycles	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20x ULN	Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20x 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 follow national Supportive care Guidelines for TMP/SMX substitutions.

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

Mucositis: For Grade 3-4 mucositis, withhold IV MTX until resolved. Increase leucovorin rescue following the next course from 3 to 5 doses on a q6 hr schedule. If subsequent course is not associated with Grade 3-4 mucositis, attempt to decrease the leucovorin. If mucositis recurs despite the extended leucovorin, decrease the dose of MTX by 25%, increase hydration to 200 mL/m^2/hr and continue increased leucovorin as above. Should subsequent courses be well tolerated, use a stepwise approach to resuming a standard approach to drug delivery. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Myelosuppression: HD MTX should be held for ANC < 750/μL and platelets < 75000/μL.

5.10 Interim Maintenance with Capizzi Methotrexate (SR Arm B: Investigational COG Arm)

Hepatic Dysfunction: Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to each dose 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 MTX
< 10 X ULN	Continue with therapy as scheduled
10 – 20 X ULN	Continue with therapy as scheduled for 1 cycle
10 – 20 X ULN for 2 consecutive cycles	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip 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 follow National Supportive care Guidelines for TMP/SMX substitutions.

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

Nephrotoxicity: Postpone course if serum creatinine is >1.5 x baseline or GFR creatinine clearance < 65 mL/1.73m^2/minute.

Mucositis: For Grade 3-4 mucositis, withhold IV MTX until resolved. Discontinue MTX dose escalation and resume at 80% of last dose if therapy is delayed for myelosuppression or Grade 3 or greater mucositis. If mucositis persist or recurs, consider culturing lesions for herpes simplex.

Myelosuppression:

i. If ANC is < 500/µL or platelets < 50, 000/µL, hold all chemotherapy and repeat blood counts in 4 days.

a. If repeat ANC ≥ 500/µL and platelets ≥ 50,000/µL, give same dose of methotrexate as previous cycle.

b. If ANC is still < 500/µL or platelets < 50,000/µL, give VCR and PEG-ASP (if Day 2 or 22) and repeat counts in 7 days. If counts are subsequently adequate, reduce dose of IV MTX by 20%. Do not make up missed dose of MTX. If counts still too low, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL.

ii. If ANC ≥ 500/µL but < 750/µL and platelets ≥ 50,000 but < 75 000/µL, give same dose of MTX as previously.

iii. If ANC ≥ 750/µL and platelets ≥ 75,000, increase MTX by 50 mg/m^2.

Prolonged cytopenia is defined as ANC < 500/μL and/or platelets < 50 000/μL after withholding therapy for > 2 weeks. Perform a bone marrow examination after 2 weeks of withholding chemotherapy, if no recovery is apparent. If monocyte count is increasing or viral myelosuppression is clinically suspected, the bone marrow examination may be postponed for 1-2 weeks and omitted if ANC and platelets fully recover by the 4th week after therapy is withheld.

5.11 PO Methotrexate (MTX) and Mercaptopurine (MP)

Interim Maintenance #1 (High dose MTX with leucovorin rescue)

If ANC is < 500/μL and/or platelets < 50,000/μL, hold mercaptopurine. Restart mercaptopurine at full dose with next dose of HD MTX when ANC is ≥ 500/µL and platelets are ≥ 50,000/µL. Do not make up missed doses. Consider a marrow evaluation in the face of persistent or prolonged cytopenias. If patient develops severe or unexpected myelosuppression, see section below on thiopurine pharmacology testing.

Maintenance:

Dose adjustements for high WBC counts and for myelosuppression (neutropenia and/or thrombocytopenia) shall be performed according to national guidelines.

Mucositis Grade 3-4: MTX should be reduced to 50% if Grade 3 toxicity develops; withhold in the presence of Grade 4 toxicity until there is a resolution, then resume at 50% of original dose with gradual dose escalation. If mucositis persists or recurs, consider culturing for herpes simplex.

Liver Dysfunction: For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain direct bilirubin. Monitor SGPT/ALT or SGOT/AST and direct bilirubin every 2 weeks during Consolidation and every 4 weeks during Maintenance as long as transaminases remain over 5x ULN.

Continue full dose therapy unless either of the following occurs:
1) Direct bilirubin > 2.0 mg/dL

2) SGPT/ALT or SGOT/AST > 20x ULN (consistent with Grade 4 toxicity) on 2 determinations at least 1 week apart.

If either of these occurs, hold MTX and monitor labs as above, weekly. Restart at full dose therapy when the transaminase is less than 5x ULN, if bilirubin is normal. If liver dysfunction persists, consider a trial period with MTX but without MP, especially if red cell MP methylated derivatives are elevated. Also consider liver biopsy.

Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in SGPT/ALT or SGOT/AST above 5x ULN.

Pharmacology Testing (TPMT and NUDT15) and Dosage Adjustments:

MP and 6-TG are methylated directly by thiopurine methyltransferase (TPMT) to an inactive metabolite. TPMT activity varies tremendously among patients, because of a common inherited genetic defect in TPMT. One in 300 patients is completely deficient (homozygous defective) and 10% of the population are moderately deficient in TPMT activity because they have inherited one variant (non-functional) TPMT allele (i.e., heterozygotes). [60-63] Patients with low TPMT form higher concentrations of the 6-thioguanine nucleotides (6-TGN) and are more susceptible to acute thiopurine toxicity (primarily myelosuppression, involving neutropenia, thrombocytopenia, and anemia). Patients with the complete deficiency of TPMT tolerate less than 10% of protocol doses of MP (10 to 30 mg/m^2/day 3 days per week). About 35% of heterozygotes require a lower dose of MP to avoid dose-limiting myelosuppression. [64]

Recently, germline variants in the gene encoding the nucleoside diphophate–linked moiety X-type motif 15 (*NUDT15*) were reported in approximately 4% of Hispanic/Native American and nearly 10% of East Asian children with ALL; these polymorphisms are strongly associated with 6-MP intolerance.[65] There are now CLIA certified tests for TPMT genotype and phenotype, NUDT15 polymorphism and for measurement of thiopurine metabolites (6-methyl mercaptopurine [6-MMP] and 6-TGN measurements). Only 3 SNPs constitute well over 90% of the inactivating mutations in the gene, based on studies in numerous racial and ethnic groups worldwide. [60,66-69] Thus, the genotyping test has a low false negative rate, and may be preferable to TPMT phenotype testing in cases where a history of red cell transfusions would potentially confound assessments of RBC TPMT activity. When the genotyping result is coupled with a phenotyping test for TPMT or with thiopurine metabolite concentrations in erythrocytes, the reliability of the tests will be even greater. Moreover, metabolite levels can provide an index of patient compliance with thiopurine therapy.

Recommendations for Thiopurine Monitoring and Dosage Adjustments:
When myelosuppression has led to significant delays in therapy (> 2 weeks) or is disproportionate to the therapy, thiopurine testing should be performed:

- For subjects who have received full dose thiopurine therapy during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict TPMT status and actual thiopurine exposure.
- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status
- TPMT genotyping will be informative in all subjects, if at least 1 mutant allele is identified. If not, and myelosuppression continues, send samples for TPMT activity and/or metabolites since TPMT genotyping will miss 5%-10% of mutants. *Genotyping can be done despite recent transfusions.*

Suggested Dose Adjustments in Subjects With Unacceptable Myelosuppression:

- If the subject is *homozygous deficient* for TPMT or NUDT15, the thiopurine dose should be *reduced to* 10-20 mg/m^2/day 3 days per week. If the subject is *heterozygous for TPMT and* has experienced significant myelosuppression, the thiopurine dose should be reduced by 30%-50%. It is not yet clear how the dose of thiopurine should be adjusted for patients who are heterozygous for NUDT15 but such patients should be monitored carefully while on thiopurines. If a patient is has two polymorphisms in NUDT15 (ie heterozygous for both the R139C and the R139H), they should be treated as

if they are homozygous deficient. Gradual dose escalations should be attempted as outlined below.

Do not increase the dose in response to a high ANC for 4 weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are not often necessary.

- If the subject is homozygous wild-type (high activity) for TPMT or NUDT15, then discontinue TMP/SMX and use pentamidine or dapsone. For modifications of the oral MP and MTX see the beginning of this section.

5.12 Steroids (Dexamethasone, PrediSO(LO)NE)

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

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

Pancreatitis: Do not modify dose for asymptomatic elevations of amylase and/or lipase. Hold steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis. Steroids may be restarted once patient's condition has improved.

Osteonecrosis (ON): Do not modify corticosteroid therapy for osteonecrosis (also referred to as avascular necrosis) during Induction or Delayed Intensification. Consider omitting Maintenance steroid for osteonecrosis Grade 1 (clinically asymptomatic, radiographic finding only). Omit Maintenance steroid for osteonecrosis Grade 2 or greater, and notify study chair. Consider resuming Maintenance steroid after 6 months if joint symptoms have resolved and if MRI findings have significantly improved or normalized.

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

Inability to take oral doses:
For dexamethasone, substitute the IV preparation mg for mg. For prednisone, substitute IV methylprednisolone at 80% of the oral prednisone dose. Note that if substituting oral prednisolone for prednisone, the doses are the same; prednisone is converted in the liver to prednisolone.

Severe infection: Do not hold or discontinue steroids during Induction IA 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."

Severe psychosis: Dexamethasone dose may be reduced by 50% for severe psychosis. If symptoms persist, consider switching to an equivalent dose of prednisone.

5.13 PO Thioguanine (TG)

Consolidation:
Oral TG should be held for suspected or proven serious infection.

For severe and/or unexpected myelosuppression, evaluate for TPMT or NUDT15 activity as described in Section 5.10.

Hold for direct bilirubin > 2.0 mg/dL. Do not make up missed doses.

5.14 Vincristine

PLEASE USE "BALIS" SCALE FOR GRADING NEUROPATHY (See text box below)

Severe neuropathic pain (Grade 3 or greater):
Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. NOTE: neuropathic pain can be not only severe but difficult to treat. However, 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.

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.

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.

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

Hyperbilirubinemia[70,71]:

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

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

Extravasation:
In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to National group guidelines.

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).
- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

6 DRUG INFORMATION

6.1 ASPARAGINASE Erwinia chrysanthemi

(Erwinia *chrysanthemi*, Erwinase®, ErwinazeTM, Crisantaspase)

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* 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 using the IM route of administration. In a multicenter study characterizing the pharmacokinetic profile of 25,000 International Units/m^2 Erwinaze® given intravenously over one hour on the same dosing schedule of Monday, Wednesday, Friday for 2 consecutive weeks, 83% (20/24) and 43% (9/21) of evaluable patients achieved an asparaginase activity level of ≥ 0.1 International Units/mL at 48 post-dose 5 and 72 hours post-dose 6, respectively. No formal drug interaction studies have been performed with asparaginase *Erwinia chrysanthemi*.

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.		

(L) Toxicity may also occur later.

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.

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

Erwinia asparaginase can be administered by intramuscular injection or by intravenous infusion. Use appropriate precautions for preparation of a hazardous agent. Visually inspect the powder in vial for foreign particles or discoloration prior to reconstitution.

For intramuscular administration, 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. 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.

For intravenous use, slowly inject the appropriate volume of reconstituted solution into a Normal Saline 100 mL infusion bag; do not shake or squeeze the bag. Infuse *Erwinia* asparaginase over 1 hour. Do not infuse other intravenous drugs through the same intravenous line while infusing *Erwinia* asparaginase.

Administer the dose within a 8 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. If not administered within 15 minutes from reconstitution withdrow the solution in a glass or polyetilene syringe.
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.

6.2 CYCLOPHOSPHAMIDE INJECTION

(Cytoxan)

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.

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 (prolonged or permanent)[1] (L)	Amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2](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.

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).

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

Cyclophosphamide for Injection:
If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution further dilute in dextrose or saline containing solutions for IV use.

6.3 CYTARABINE - ALL ROUTES

(Cytosine arabinoside, Ara-C, Cytosar®)

Source and Pharmacology:
Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase $t_{½}$ of about 10 minutes, with a secondary elimination phase $t_{½}$ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration. Intrathecally administered doses are metabolized and eliminated more slowly with a $t_{½}$ of about 2 hours.

Toxicity: (Intravenous, SubQ, IM)

	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 *With High Dose*: conjunctivitis	Flu-like symptoms with fever, rash	Ara-C syndrome (fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, malaise, conjunctivitis), anaphylaxis, swelling, pain and redness at the site of the medication injection (SubQ or IM injection) *With High Dose:* cardiomyopathies (vasculitis, and pericarditis), cerebral and cerebellar dysfunction including: encephalopathy, aseptic meningitis, ataxia, dysphasia, nystagmus, a decreased level of consciousness, personality changes, somnolence, seizures
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (anemia, thrombocytopenia, leukopenia, megaloblastosis, reticulocytopenia), stomatitis, alopecia	Diarrhea, hypokalemia, hypocalcemia, hyperuricemia *With High Dose*: capillary pulmonary leak syndrome (RDS, pulmonary edema)	Hepatotoxicity, sinusoidal obstruction syndrome (SOS, formerly VOD), urinary retention, renal dysfunction, pain and erythema of the palms and soles
Delayed: Any time later during therapy, excluding the above conditions			Asymptomatic nonoliguric rhabdomyolysis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cytarabine have been noted in humans. It is unknown whether the drug is excreted in breast milk.		

Toxicity: (Intrathecal)

	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, fever, headache	Arachnoiditis	Rash, somnolence, meningismus, convulsions, paresis
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia
Delayed: Any time later during therapy, excluding the above condition			Necrotizing leukoencephalopathy, paraplegia, blindness (in combination with XRT & systemic therapy)

Formulation:

Cytarabine for Injection is available in vials of 100 mg, 500 mg, 1 g, and 2 g containing a sterile powder for reconstitution. It is also available at a 20 mg/mL concentration with benzyl alcohol (25 mL per vial) or as a preservative free solution (5 mL, 50 mL per vial), and at a 100 mg/mL concentration with benzyl alcohol (20 mL vial) or as preservative free solution (20 mL vial). Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Cytarabine solutions should be protected from light.

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

IV Infusion:
Reconstitute the lyophilized powder with Bacteriostatic Water for Injection or NS injection. Solution containing bacteriostatic agent should not be used for the preparation of doses > 200 mg/m^2. May be further diluted with dextrose or sodium chloride containing solutions. May give by IV push injection, by IV infusion, or by continuous infusion.

Low Dose (≤ 200 mg/m²/dose): For administration by IV push, reconstitute to a concentration of 20-100 mg/mL.

High Dose (≥ 1000 mg/m²/dose): Administer steroid eye drops (dexamethasone or prednisolone), 2 drops each eye q6h beginning immediately before the first dose and continuing 24 hours after the last dose. If patient does not tolerate steroid eye drops, administer artificial tears on a q2-4 hour schedule.

Stability: When reconstituted with Bacteriostatic Water for Injection, cytarabine is stable for 48 hours at room temperature. Solutions reconstituted without a preservative should be used immediately. Discard if solution appears hazy. Diluted solutions in D5W or NS are stable for 8 days at room temperature; however, the diluted cytarabine should be used within 24 hours for sterility concerns.

NOTE

Intrathecal:
For intrathecal administration, dilute with 5-10 mL (or volume per institutional practice) preservative free 0.9% sodium chloride injection, lactated Ringer's injection, Elliot's B solution. The volume of CSF removed should be equal to at least ½ the volume delivered.

Patient Age (years)	Recommended volume	10% CSF volume	CSF Volume *
1 – 1.99	5 – 10 mL	5 Ml	50 ± 10 mL (babies)
2 – 2.99	5 – 10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	5 – 10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	5 – 10 mL	13 mL	130 ± 30 mL (adults)

*Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8

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 cytarabine mixed in NS, lactated Ringer's injection, or Elliot's B solution is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

6.4 DAUNORUBICIN

(Daunomycin, rubidomycin, Cerubidine®)

Source and Pharmacology:

Daunorubicin is an anthracycline antibiotic isolated from cultures of *Streptomyces coeruleorubidus*. Daunorubicin is closely related structurally to doxorubicin only differing in that the side chain of daunorubicin terminates in a methyl group rather than an alcohol. The cytotoxic effect of daunorubicin on malignant cells and its toxic effects on various organs are similar to those of doxorubicin and are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of daunorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of cytocidal activity. Daunorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of daunorubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•) which may lead to DNA damage or lipid peroxidation. Daunorubicin is metabolized more rapidly by aldoketoreductases to the active metabolite, daunorubicinol, than is doxorubicin. Daunorubicin hydrochloride is rapidly and widely distributed in tissues, with the highest levels in the spleen, kidneys, liver, lungs, and heart. Daunorubicin serum decay pattern is multiphasic. The initial $t_{½}$ is approximately 45 minutes followed by a terminal $t_{½}$ of 18.5 hours. By 1 hour after drug administration, the predominant plasma species is daunorubicinol, which disappears with a half-life of 26.7 hours. Twenty five percent of an administered dose of daunorubicin is eliminated in an active form by urinary excretion and an estimated 40% by biliary excretion.

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, sclerosis of the vein	Diarrhea, anorexia, abdominal pain, extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, rash, 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, myocarditis-pericarditis syndrome, conjunctivitis and lacrimation
Delayed: Any time later during therapy			Cardiomyopathy[1] (uncommon at cumulative doses ≤ 550 mg/m², 400 mg/m² with mediastinal radiation, 300 mg/m² in children, or 10 mg/kg in children < 2 yrs or 0.5 m²) (L), hyper-pigmentation of nail beds
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 toxicities and teratogenic effects of daunorubicin have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

[1] *Risk increases with cardiac irradiation, exposure at a young or advanced age.*

(L) Toxicity may also occur later.

Formulation and Stability:
Daunorubicin is available as red-orange lyophilized powder[1] for injection in 20 mg single dose vials and a preservative free 5 mg/mL solution[2] in 20 mg (4 mL) and 50 mg (10 mL) vials.

Powder for Injection:
Store intact, unreconstituted vials at room temperature, 15°-30°C (59°-86°F). Protect from light. Retain in carton until contents are used. Reconstitute a 20 mg vial with 4 mL SWFI to a final concentration of 5 mg/mL. After adding the diluent, the vial should be shaken gently and the contents allowed to dissolve. The reconstituted solution is stable for 24 hours at room temperature and 48 hours refrigerated. Protect from exposure to sunlight.

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

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

Administer by IV side arm into a rapidly flowing infusion solution. Alternately, daunorubicin may be further diluted in saline or dextrose containing solutions and administered by infusion. Protect final preparation from light. To avoid extravasation, the use of a central line is suggested.

6.5 DEXAMETHASONE

(Decadron®, Hexadrol®, Dexone®, Dexameth®)

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 (Tlymphocytes), 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 Tlymphocyte 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 halflife is 36-72 hours. It is primarily metabolized in the liver and excreted by the kidneys.

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), pituitary-adrenal axis 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 during therapy	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia	Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis[1] (L)
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of dexamethasone in children)	
Unknown Frequency and Timing:	**Fetal and teratogenic toxicities**: 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.		

[1] ***Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003; 17: 541-6.***

(L) Toxicity may also occur later.

Formulation and Stability:

Oral:

Available in 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg tablets; liquid formulations are available in 0.5 mg/5 mL and 1 mg/1 mL concentrations. 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.

Injection:

Dexamethasone Sodium Phosphate Solution for Injection is available as 4 mg/mL (1 mL, 5 mL, and 30 mL vials) and 10 mg/mL (1 mL and 10 mL vial sizes). Vials are available in multi-dose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium citrate, sodium hydroxide to adjust pH, Water for Injection, sodium sulfite, bisulfite and metabisulfite, methyl and propyl paraben, benzyl alcohol, and EDTA.

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

Dexamethasone Sodium Phosphate for Injection may be given IV, or IM undiluted. For IV use, it may be further diluted in dextrose or saline containing solutions. Avoid using benzyl alcohol-containing dexamethasone solutions 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.

6.6 DOXORUBICIN

(Adriamycin®)

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 $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ 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.

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.

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.

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.

6.7 ETOPOSIDE - INJECTION

(VePesid®, Etopophos®,VP-16)

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 G_2 phase of the cell cycle. The initial $t_{½}$ 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/m^2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m^2. 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.

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 urticaria	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.		

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.

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

Etoposide:
Dilute etoposide to a final concentration 0.2-0.4 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 0.10.4 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.

6.8 FILGRASTIM, TBO-FILGRASTIM, FILGRASTIM-SNDZ

(Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®, Granix®, Zarxio®)

Source and Pharmacology:

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor, which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). Filgrastim exhibits nonlinear pharmacokinetics with clearance dependent on filgrastim concentration and neutrophil count. Filgrastim is cleared by the kidney. The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2-8 hours.

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		Local irritation at the injection site, headache	Allergic reactions (more common with IV administration than subq):skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, rash or exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			Cutaneous vasculitis, ARDS
Late: Anytime after completion of treatment			MDS or AML (confined to patients with severe chronic neutropenia and long term administration)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:

Neupogen® supplied as a clear solution of 300 mcg/mL in 1 mL or 1.6 mL vials. Neupogen® vials are preservative free single use vials. Discard unused portions of open vials.

Neupogen®, Granix®, and Zarxio® are also available as single use prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim for subcutaneous administration.
Store refrigerated at 2º-8ºC (36º-46ºF). Protect from light. Do not shake. Prior to injection, filgrastim and filgrastim-sndz may be allowed to reach room temperature for a maximum of 24 hours (infusion must be completed within 24 hours of preparation). TBO-filgrastim may be removed from 2°C-8°C (36°F-46°F) storage for a single period of up to 5 days between 23°C to 27°C (73°F to 81°F). Avoid freezing and temperatures > 30ºC.

For IV use, dilute filgrastim (Neupogen®) and tbo-filgrastim (Granix®) in D5W only to concentrations > 15 mcg/mL. Filgrastim-sndz (Zarxio®) may be diluted in D5W to concentrations between 5 mcg/mL and 15 mcg/mL. At concentrations below 15 mcg/mL, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/mL) in order to minimize the adsorption of filgrastim to plastic infusion containers and equipment for all 3 products (communication on file from Teva Pharmaceuticals USA). Filgrastim or filgrastim-sndz dilutions of 5 mcg/mL or less are not recommended. Tbo-filgrastim dilutions below 2 mcg/mL are not recommended. Diluted filgrastim biosimilar products should be stored at 2º-8ºC (36º-46ºF) and used within 24 hours. Do not shake.

Do not dilute with saline-containing solutions at any time; precipitation will occur.

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

Filgrastim biosimilar products should not be administered within 24 hours of (before AND after) chemotherapy.

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

6.9 IFOSFAMIDE

(Isophosphamide, Iphosphamide, Z4942, Ifex®)

Source and Pharmacology:
Ifosfamide is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation (P450 3A isoenzymes) for the production of the reactive 4-hydroxyoxazaphorine intermediate which serves as a carrier molecule for the ultimate intracellular liberation of acrolein and phosphoramide mustard which is an active bifunctional alkylating species. Acrolein is thought to be the cause of the hemorrhagic

cystitis as seen with cyclophosphamide. Ifosfamide demonstrates dose-dependent pharmacokinetics whereby the terminal half-life ranges from 7 to 16 hours at doses of 1.6-2.4 g/m² to 3.8-5 g/m², respectively. At 1.62.4 g/m²/d, 12 to 18% of the dose was excreted as unchanged drug in the urine, whereas at a 5 g/m² single-dose, 61% was excreted in the urine as the parent drug. Evidence also exists to suggest that ifosfamide metabolism is inducible, with more rapid clearance occurring in the second and later doses when a course of therapy is given as fractionated doses over 3 to 5 days. There is more chloroethyl side chain oxidation of ifosfamide (up to 50%) than of cyclophosphamide (< 10%), and the degree of such metabolism is more variable than with cyclophosphamide. Oxidation of the chloroethyl groups produces chloroacetaldehyde, which is thought to be responsible for the neurotoxicity and renal toxicity that have been seen with ifosfamide therapy.

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 (acute and delayed)	CNS toxicity (somnolence, depressive psychosis and confusion)	Anorexia, diarrhea, constipation, encephalopathy which may progress to coma (L), seizure, SIADH, phlebitis, hypokalemia
Prompt: Within 2-3 weeks, prior to next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, cardiac toxicities (arrhythmia, asymptomatic ECG changes), microscopic hematuria, metabolic acidosis	↑ liver enzymes, ↑ bilirubin, hemorrhagic cystitis with macroscopic hematuria, dysuria, cystitis and urinary frequency (< 5% with mesna and vigorous hydration) (L), bladder fibrosis
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)		Renal failure acute or chronic, renal tubular acidosis, Fanconilike syndrome gonadal dysfunction, ovarian failure[1] (L), CHF
Late: Any time after completion of treatment	Moderate nephrotoxicity (↓ in glomerular filtration rate, renal tubular threshold for phosphate, and serum bicarbonate)		Secondary malignancy, hypophosphatemic rickets
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of ifosfamide have been noted in animals. Ifosfamide is excreted into breast milk.		

[1] *Dependent on dose, age, gender and degree of pubertal development at time of treatment*
(L) Toxicity may also occur later.

Formulation and Stability:
Ifosfamide is available in 1 g and 3 g single dose vials of lyophilized white powder without preservatives and as a 50 mg/mL solution in 20 mL and 60 mL vials.

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

Reconstitute ifosfamide lyophilized powder with sterile water for injection or bacteriostatic water for injection(use 20 mL for the 1 g vial and 60 mL for the 3 g vial) to produce a final

concentration of 50 mg/mL. **Use sterile water for injection without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.** Although the reconstituted product is stable for 7 days at room temperature and up to 6 weeks under refrigeration, the manufacturer recommends refrigeration and use within 24 hours to reduce the possibility ofmicrobial contamination. Store unreconstituted vials at room temperature 20°-25°C (68°-77°F). Protect from temperatures above 30°C (86° F). Ifosfamide may liquefy at temperatures > 35 C.

Reconstituted solutions of ifosfamide or ifosfamide solution should be diluted further to concentrations of 0.6 to 20 mg/mL in dextrose or saline containing solutions. Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags or PAB bags, are physically and chemically stable for 1 week at 30°C (86°F) or 6 weeks at 5°C (41°F). The manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination.

Mesna must always be administered in conjunction with ifosfamide. Adequate hydration is required. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Refer to the Chemotherapy Administration Guidelines for additional information.

6.10 IMATINIB MESYLATE

(Gleevec®, STI-571)

Source and Pharmacology: Imatinib (STI571), a phenylaminopyrimidine derivative, is a selective inhibitor of the tyrosine kinase activity of the *BCR-ABL1* fusion gene (oncoprotein), the product of the Philadelphia chromosome. Imatinib mesylate has also shown high activity in blocking the tyrosine kinase activity of c-kit (stem-cell factor receptor) (SCF) and platelet-derived growth factor receptor (PDGF). The ability of imatinib to inhibit *BCR-ABL1* tyrosine kinase activity is related to its occupancy of the kinase pocket of the protein, which blocks access to ATP and prevents substrate phosphorylation inhibiting Bcr- Abl dependent cellular proliferation. Imatinib has caused apoptosis or arrest of growth in hematopoietic cells expressing *BCR-ABL1*.

Imatinib is well-absorbed after oral administration; maximum plasma concentrations are achieved 2 to 4 hours after administration. The elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. The elimination half-life of the parent drug in children is approximately 15 hours. Imatinib is approximately 95% protein-bound, mostly to albumin and alpha-1-acid glycoprotein. CYP3A4 is the major enzyme responsible for metabolism. CYP1A2, CYP2D6, CYP2C9, and CYP2C19 play minor roles in metabolism. Drugs metabolized by these same enzymes should be avoided or used with caution to avoid unwanted drug interactions. Severe hepatic impairment (bilirubin >3-10 times ULN) increases AUC by 45% to 55% for imatinib and its active metabolite, respectively. Elimination is predominately in the feces, mostly as metabolites.

Toxicities:

Incidence	Toxicities
Common (>20% of patients)	• **Nausea, vomiting, diarrhea** • **Abdominal pain** • **Fluid retention/edema** • **Fatigue/weakness** • **Rash** • **Myalgia** • **Arthralgia** • **Muscle cramps** • **Musculoskeletal or joint pain** • **Headache** • **Infection**
Occasional (4-20% of patients)	• **Fever** • **Rigors/chills** • **Flu-like symptoms** • **Hemorrhage** • **Anemia** • **Neutropenia/leukopenia** • **Thrombocytopenia** • **Dyspepsia/heartburn** • **Flatulence** • **Dizziness** • **Insomnia** • **Constipation** • **Night sweats** • **Weight gain** • **Dysgeusia** • **Anorexia** • **Dysphagia/odynophagia** • **Mucositis/stomatitis** • **Esophagitis** • **Cough** • **Epistaxis** • **Pruritis** • **Ascites** • **Paresthesias** • **Pigmentation changes (vitiligo)** • **Alopecia** • **Hypokalemia** • **Hypoalbuminemia** • **Hypophosphatemia** • **Hypeglycemia** • **Lymphopenia** • **Alanine aminotransferase increased** • **Aspartate aminotransferase increased** • **Alkaline phosphatase increased** • **Bilirubin increased** • **Creatinine increased**

Rare (<3% of patients)	• **Angioedema** • **Increased intracranial pressure/ cerebral edema** • **Dehydration** • **Hepatotoxicity** • **Pleural effusion, pulmonary edema, pneumonitis, dyspnea** • **Pericardial edema** • **Exfoliative dermatitis** • **Steven Johnson Syndrome** • **Erythema Multiforme** • **DRESS syndrome (fever, severe skin eruption, lymphadenopathy, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement)** • **Conjunctivitis, blurred vision, dry eye** • **Thrombosis/thromboembolism** • **Left ventricular systolic dysfunction** • **Tumor lysis syndrome** • **Growth retardation in children***
Pregnancy & Lactation	Pregnancy category D. Adverse events have been observed in animal reproduction studies. Women of childbearing potential are advised not to become pregnant (female patients and female partners of male patients); highly effective contraception is recommended. Case reports of pregnancies while on therapy (both males and females) include reports of spontaneous abortion, minor abnormalities (hypospadias, pyloric stenosis, and small intestine rotation) at or shortly after birth, and other congenital abnormalities including skeletal malformations, hypoplastic lungs, exomphalos, kidney abnormalities, hydrocephalus, cerebellar hypoplasia, and cardiac defects. Imatinib and its active metabolite are found in human breast milk. Due to the potential for serious adverse reactions in the breast-feeding infant, the manufacturer recommends a decision be made to discontinue breast-feeding or to discontinue the drug, taking into account the importance of treatment to the mother.

* Growth retardation has been reported in children receiving imatinib; generally when treatment was initiated in prepubertal children growth velocity was usually restored as pubertal age was reached. Monitor growth closely.

Formulation and Stability: Imatinib Mesylate is available as 100 mg and 400 mg tablets. Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from moisture.

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

Doses ≤600 mg should be given once daily; all doses > 600 mg dose should be given divided twice daily. Maximum dose is 800 mg, which should be administered as 400 mg twice daily. Whenever possible, the 400 mg tablets should be used to reduce iron exposure (tablets are coated with ferric oxide). See Appendix VI: Imatinib Dosing Guidelines.

If patient cannot swallow the tablet whole, an oral suspension may be prepared by placing tablets (whole, do not crush) in a glass of water or apple juice. Use ~50 mL for 100 mg tablet, or ~200 mL for 400 mg tablet. Stir until tablets are disintegrated, then administer immediately. To ensure the full dose is administered, rinse the glass and administer residue.

A 40 mg/mL oral suspension may be prepared using imatinib 400 mg tablets and Ora-Sweet. Determine necessary quantity of imatinib 400 mg tablets; crush the tablets in a glass mortar and triturate to a fine powder (estimated powder volume for each imatinib 400 mg tablet is 0.4 mL). Measure the necessary volume of Ora-Sweet (to make a 40 mg/mL suspension) and add to the powder by geometric dilution until a smooth suspension is created. Transfer to an amber plastic bottle and label "Shake Well Before Use" and "Use by (date)". Suspension is stable for up to 14 days at both room temperature and 4°C (39.2°F). [72]

Imatinib is a local irritant and must be taken in an upright position with a meal or a large glass (or bottle, for younger children) of water (240 ml/8 oz; at least 4 oz for children ≤ 3 years of age). Children ≤ 3 years of age should remain in an upright position for 30 minutes post-administration to prevent esophageal irritation.

If the patient vomits after taking the drug, the dose is replaced only if the tablets can actually be seen and counted. The number of tablets counted is to be replaced. For younger children who take the drug dissolved in water or apple juice, replace the dose only if the vomiting has occurred directly after swallowing and if the amount appears substantial.

Hazardous agent: Use appropriate precautions for handling and disposal of imatinib.

Supplier: Commercially available. See prescribing information.

6.11 LEUCOVORIN CALCIUM

(LCV, Wellcovorin®, citrovorum factor, folinic acid)

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.

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, urticaria, 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.		

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/m^2 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. For levoform (instead of racemic) the dose should be half.

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.

6.12 INTRATHECAL TRIPLES

(Methotrexate/Hydrocortisone/Cytarabine, IT-3)

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 $t_{½}$ of 4.5 and 14 hours respectively. Following IT injection of cytarabine the elimination of the drug from the CSF is biphasic with a $t_{½}$ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

Intrathecal Triple Therapy (Methotrexate/ Hydrocortisone/Cytarabine)
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, 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.*

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 succinate 100 mg vial sterile powder for injection.

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.

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.

6.13 MERCAPTOPURINE

(6-MP, Purinethol®, Xaluprine®, Purixan™, 6-mercaptopurine)

Source and Pharmacology:
Mercaptopurine is an analogue of the purine bases adenine and hypoxanthine. The main intracellular pathway for MP activation is catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) which catalyzes the conversion of MP to several active nucleotide metabolites including thioinosinic acid, a ribonucleotide which can interfere with various metabolic reactions necessary for nucleic acid (RNA and DNA) biosynthesis. It can also cause pseudofeedback inhibition of the first step in de novo purine biosynthesis or convert to another ribonucleotide which can cause feedback inhibition. Mercaptopurine can be incorporated into DNA in the form of TG nucleotides as well and thus produce toxicity. The absorption of an oral dose of MP is incomplete and variable, with only about 16%-50% of an administered dose reaching the systemic circulation secondary to a first pass metabolism in the liver. Food intake and co-administration with cotrimoxazole (TMP/SMX) significantly reduces absorption of MP. After IV administration, MP has a plasma half-life of 21 minutes in children and 47 minutes in adults. Approximately 19% is bound to protein. Mercaptopurine is well distributed into most body compartments except the CSF. (With high dose IV MP the CSF to plasma ratio is 0.15.) MP is metabolized by xanthine oxidase in the liver to 6-Thiouric acid an inactive metabolite. In patients receiving both MP and allopurinol (a xanthine oxidase inhibitor) the dose of MP must be reduced by 50-75%. Since TPMT, 6-thiopurine methyltransferase, is also one of the enzymes involved in the metabolism of MP, those individuals who have an inherited deficiency of the enzyme may be unusually sensitive to the myelosuppressive effects of MP and prone to develop rapid bone marrow suppression following the initiation of treatment. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

Toxicity:

Incidence	Toxicities
Common (>20% of patients)	Anemia, neutrophil count decreased, white blood cell decreased, platelet count decreased
Occasional (4 - 20% of patients)	Anorexia, diarrhea, nausea, vomiting, erythematous rash, malaise, oligospermia
Rare (≤3% of patients)	Urticaria, skin hyperpigmentation, alopecia, hyperuricemia, hepatic failure, hepatic necrosis, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, pulmonary fibrosis, secondary malignant neoplasm

Incidence	Toxicities
Pregnancy and Lactation	**Pregnancy Category D** Mercaptopurine can cause fetal harm, including an increased incidence of abortion and stillbirth. Advise women to avoid becoming pregnant while receiving mercaptopurine. Mercaptopurine was embryo-lethal and teratogenic in several animal species (rat, mouse, rabbit, and hamster). It is not known whether mercaptopurine is excreted in human milk; breastfeeding should be avoided.

Formulation and Stability:

Mercaptopurine is available as a 50 mg tablet containing mercaptopurine and the inactive ingredients corn and potato starch, lactose, magnesium stearate, and stearic acid. Store at 15°25°C (59°77°F) in a dry place. In the United States, mercaptopurine is also available as an oral suspension in a concentration of 20 mg/mL (2000 mg/100 mL per bottle). The oral suspension is a pink to brown viscous liquid supplied in amber glass multiple-dose bottles with a child resistant closure. It should be stored at 15°25°C (59°77°F) in a dry place.

NOTE: the concentration of the commercially available suspension (20 mg/mL) and the compounded suspension (50 mg/mL) are NOT the same; doses should be prescribed in the milligrams required, not mL.

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

Recent studies have demonstrated no differences in absorption of oral mercaptopurine when delivered on an empty or full stomach. Rather, the critically important guideline is to deliver the dose at the same time of day.[73] If allopurinol is also given, the oral dose of mercaptopurine should be reduced by 67-75%. Patients with severe myelosuppression should have their thiopurine S-methyltransferase (TPMT) or NUDT15 status and/or their thiopurine metabolite concentrations evaluated, so that the dose of mercaptopurine can be reduced in patients with a TPMT defect. Patients with the rare homozygous deficient TPMT phenotype may tolerate only 1/10th to 1/20th the average mercaptopurine dose. TPMT testing and thiopurine metabolite measurements are commercially available. Patients with homozygous deficient NUDT15 phenotype should be initiated at 20% of full dose mercaptopurine.

Suspension:
For children unable to swallow the tablets whole:
XALUPRINE® (mercaptopurine) oral suspension is supplied as a commercially available 2000 mg/100 mL (20 mg/mL) pink to brown viscous liquid in amber glass multiple-dose bottles. The suspension contains the following inactive ingredients: xanthan gum, aspartame, concentrated raspberry juice, sucrose, methyl parahydroxybenzoate, propyl parahydroxybenzoate and purified water. Once opened, XALUPRINE ® should be used within 6 weeks. Store between 15 to 25ºC (59º to 77ºF) in a dry place. Alternatively, if commercial suspension is unavailable, a 50 mg/mL oral suspension can be compounded. The suspension is prepared by crushing 50 mercaptopurine 50 mg tablets in a mortar and adding 8.5 mL sterile water for irrigation. The mixture is triturated to form a smooth paste. Next, 16.5 mL simple syrup (pH=7) are added with continuous mixing and finally cherry syrup (pH=7.1) is added to a total volume of 50 mL. The suspension is stable in amber glass bottles at room temperature (19ºC -23ºC) for up to 5 weeks. The suspension should be

shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension.[74]

6.14 MESNA

(sodium 2-mercaptoethane sulfonate, UCB 3983, Mesnex®)

Source and Pharmacology:
Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide. Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys. In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites. In multiple human xenograft or rodent tumor model studies, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

After an 800 mg dose the half lives for mesna and dimesna are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours.

Toxicity[1]:

	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, stomach pain, fatigue, headache	Facial flushing, fever, pain in arms, legs, and joints, rash, transient hypotension, tachycardia, dizziness, anxiety, confusion, periorbital swelling, anaphylaxis, coughing
Prompt: Within 2-3 weeks, prior to the next course		Diarrhea	
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of mesna have not been noted in animals fed 10 times the recommended human doses. There are however no adequate and well-controlled studies in pregnant women. It is not known if mesna or dimesna is excreted into human milk		

[1]*All currently available products in the U.S. are preserved with benzyl alcohol. Benzyl Alcohol has been associated with death in pre-term infants weighing less than 2500 g and receiving 99-405 mg/kg/day. Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. In pre-term infants, however, this metabolic pathway may not be well developed. Onset of toxic illness in these infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping*

respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension leading to cardiovascular collapse was a late finding usually preceding death. [For comparison in the ICE regimen of 3000 mg/m²/day of ifosfamide and a daily mesna dose of 60% of the ifosfamide dose = to 1800 mg/m²/day; a child would be expected to receive 18 mL/m²/day of mesna (concentration of 100 mg/mL and 10.4 mg/mL of benzyl alcohol) 187.2 mg/m²/day of benzyl alcohol or 6.24 mg/kg/day.]

Formulation and Stability:
Mesna for injection is available as 100 mg/mL in 10 mL multidose vials which contain 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. Mesna Injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. Store product at controlled room temperature 15°-25°C (68-77°F). Mesna is not light-sensitive, but is oxidized to dimesna when exposed to oxygen. Mesna as benzyl alcohol-preserved vials may be stored and used for 8 days.

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

For IV administration, dilute mesna to 20 mg/mL with dextrose or saline containing solutions. Mesna may be mixed with ifosfamide or cyclophosphamide. After dilution for administration, mesna is physically and chemically stable for 24 hours at 25ºC (77ºF). Mesna may cause false positive test for urinary ketones.

6.15 METHOTREXATE - All Routes

(MTX, amethopterin, Trexall®)

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 815 hours. About 50% is bound to protein. After oral administration, approximately 60% of a 30 mg/m^2 dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. At doses > 30 mg/m^2 absorption decreases significantly. Even at low doses absorption may be very erratic, varying between 23% and 95%. 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/m^2, 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 ascitic 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.

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	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.		

[1] *May be enhanced by HDMTX and/or cranial irradiation.*
(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:		Cognitive disturbances (L)[1,]	Leukoencephalopathy[1] (L)

Any time later during therapy, excluding the above condition		learning disability (L)[1]	
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.

Formulation & Stability:
Methotrexate for oral use is available as 2.5 mg, 5 mg, 7.5 mg, 10 mg and 15 mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: anhydrous lactose, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, sodium carbonate monohydrate, talc and titanium dioxide and various dyes. Store at controlled room temperature 15°-30°C (59°-86°F) and protect from light.
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 20-25ºC (68-77ºF); excursions permitted to 15 -30ºC (59- 86 F). Protect from light

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

Oral administration: Methotrexate injection diluted in water can be used for oral administration (Marshall PS, Gertner E. Oral administration of an easily prepared solution of injectable methotrexate diluted in water: a comparison of serum concentrations vs methotrexate tablets and clinical utility.[75]

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 ≤ 25mg/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 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 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.

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.

6.16 PEG-L-Asparaginase

(PEG-asparaginase, PEGLA, PEG-L-asparaginase, polyethylene glycol-L-asparaginase, Oncaspar®)
Source and Pharmacology:
PEG-L_asparaginase 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 PEG-L_asparaginase 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 naive 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 PEG-L_asparaginase. 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 Lasparaginase (25000 IU/m2), or Erwinia (25000 IU/m2), the plasma half-lives for the three forms of Lasparaginase 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 Lasparaginase 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.

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.

Formulation and Stability:
Each milliliter of PEG-L-Asparaginase 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. PEG-L-Asparaginase admixed in 100 mL of NS or D5W is stable for 48 hours at room temperature. PEG-L-Asparaginase 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 or 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.

6.17 PEGFILGRASTIM

(pegylated filgrastim, PEG filgrastim, SD/01, Neulasta®)

Source and Pharmacology:
Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

After subcutaneous injection the elimination half-life of pegfilgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period postchemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination. After subcutaneous administration at 100 mcg/kg in 37 pediatric patients with sarcoma, the terminal elimination half-life was 30.1 (+/- 38.2) hours in patients 0 to 5 years-old, 20.2 (+/- 11.3) hours in patients 6 to 11 years-old, and 21.2 (+/- 16) hours in children 12 to 21 years-old.

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		Local irritation at the injection site (pain, induration, and local erythema), headache	Low grade fever, allergic reactions (anaphylaxis, angioedema, or urticaria), generalized erythema and flushing,
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, sickle cell crises in patients with sickle cell disease (SCD), excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			ARDS
Unknown frequency and timing:	Fetal toxicities and teratogenic effects of pegfilgrastim in humans are unknown. Conflicting data exist in animal studies. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with 27 g, ½ inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains drug natural rubber (a derivative of latex). Store refrigerated at 2°-8ºC (36º46ºF) and in the carton to protect from light. Prior to injection, pegfilgrastim may be allowed to reach room temperature protected from light for a maximum of 48 hours. Avoid freezing.

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

Pegfilgrastim should not be administered in the period between 2 weeks before and 24 hours after chemotherapy. Do not shake. The manufacturer does not recommend use of the 6-milligram (mg) fixed-dose formulation of pegfilgrastim in infants, children, or adolescents under 45 kilograms.

6.18 PREDNISONE

(Deltasone, Meticorten, Orasone®, Liquid Pred, Pediapred®, Sterapred®)

Source and Pharmacology:
Prednisone is a synthetic compound closely related to hydrocortisone. 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. Peak blood levels occur within 2 hours of oral intake. Prednisone is approximately 75% protein bound with a plasma $t_{½}$ of 3.2 to 4 hours. (Biologic half-life is 12-36 hours.)

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), pituitary-adrenal axis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema	Pancreatitis (L), electrolyte imbalance (Na retention, hypokalemia, hypocalcemia) (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed: Any time later during therapy	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia	Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis[1] (L)
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of prednisone in children)	
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: Corticosteroids cross the placenta (prednisone has the poorest transport). 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. Prednisone is excreted into breast milk in humans; however, several studies suggest that amounts excreted in breast milk are negligible with prednisone doses ≤ 20 mg/day.		

[1] ***Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003; 17: 541-6.***
(L) Toxicity may also occur later.

Formulation and Stability:
Available in 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets. Also available as a solution in 1 mg/1 mL or 5 mg/mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include calcium or magnesium stearate, corn starch, lactose, erythrosine sodium, mineral oil, sorbic acid, sucrose, talc and various dyes. The solution may include 5-30% alcohol, fructose, sucrose, saccharin, and sorbitol.

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

6.19 THIOGUANINE

(6-thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, WR-1141, Tabloid®, Lanvis®)

Source and Pharmacology:
Thioguanine is a purine analogue of the nucleic acid guanine with the substitution of a thiol group in place of the hydroxyl group on guanine. The main intracellular pathway for 6-TG activation is catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) which catalyzes the conversion of 6-TG to the active nucleotide, 6-thioguanylic acid. The monophosphate nucleotide form of 6-TG inhibits *de novo* purine synthesis and purine interconversion reactions, whereas the nucleotide triphosphate metabolite is incorporated directly into nucleic acids. Incorporation of fraudulent nucleotides into DNA interferes with DNA replication and results in the formation of DNA strand breaks. The net consequence of its action is a sequential blockade of the synthesis and utilization of the purine nucleotides. The relative contribution of each of these actions to the mechanism of cytotoxicity of 6-TG is unclear. The absorption of an oral dose of 6-TG is incomplete and variable, averaging approximately 30% of the administered dose (range: 14% to 46%).

6-TG undergoes deamination by the enzyme guanine deaminase resulting in 6-thioxanthene, which is then oxidized by xanthine oxidase to 6-thiouric acid. In contrast to mercaptopurine, 6-TG is not a direct substrate for xanthine oxidase. Because the inhibition of xanthine oxidase results in the accumulation of 6-thioxanthene, an inactive metabolite, adjustments in 6-TG dosage are not required for patients receiving allopurinol. Since TPMT, 6-thiopurine methyltransferase, is one of the enzymes involved in the deactivation of 6-TG, those individuals who have an inherited deficiency of the enzyme may be unusually sensitive to the myelosuppressive effects of 6-TG and prone to developing rapid bone marrow suppression following the initiation of treatment.

Peak levels occur 2 to 4 hours after oral administration with a median half-life is about 90 minutes (range: 25-240 minutes). Very little unchanged drug is excreted renally.

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, diarrhea, malaise	Urticaria, rash, hyperuricemia
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression		Toxic hepatitis (L), increased SGOT (AST)/SGPT (ALT), ataxia, mucositis
Delayed: Anytime later during therapy			Hepatic fibrosis(L), sinusoidal obstruction syndrome (SOS, formerly VOD) (L), hyperbilirubinemia
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of thioguanine have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

(L) Toxicity may also occur later.

Formulation and Stability:
Each greenish-yellow, scored tablet contains 40 mg thioguanine. Store at 15°-25°C (59°-77°F) in a dry place.

For patients unable to swallow tablets, a 20 mg/mL oral suspension may be compounded. Crush fifteen (n=15) 40 mg tablets in a mortar and reduce to a fine powder. Add 10 mL methylcellulose 1% in incremental proportions and mix to a uniform paste. Transfer to a graduated cylinder, rinse mortar with simple syrup, and add quantity of simple syrup sufficient to make 30 mL. Dispense in an amber glass bottle and label "shake well" and "refrigerate". If methylcellulose is not available, substitute 15 mL of Ora-Plus in place of the methylcellulose and qs with Ora-Sweet (in place of simple syrup) to a final volume of 30 mL. Both preparations are stable for 63 days at 19°C – 23°C. (Aliabadi HM, Romanick M, Somayah V, et al. Stability of compounded thioguanine oral suspensions. *Am J Health Syst Pharm* 2011;68:1278. Dressman JB, Poust RI. Stability of Allopurinol and Five Antineoplastics in Suspension. *Am J Hosp Pharm* 1983;40(4):616-8.)

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

Administer on an empty stomach, preferably at bedtime.

Substantial dosage reductions may be required in patients with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) due to accumulation of active thioguanine metabolites resulting in a higher incidence of myelosuppression.

6.20 VINCRISTINE SULFATE

(Oncovin®, VCR, LCR)

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.

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, foot drop, abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (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.		

Formulation and Stability:
Vincristine is supplied in 1 mL and 2 mL vials in which each mL 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.

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."

7 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. 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 where explicitly prohibited within the protocol).

7.1 End of Therapy & Follow-up

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

STANDARD RISK PATIENTS ONLY* STUDIES TO BE OBTAINED	End of Therapy (EOT)	3 years post-EOT
Height, Weight, Body surface area	X	X
Echocardiogram (or radionucleide ventriculography)	X	X
Bone age**	X	X

*** Studies to be obtained in SR patients treated who completed protocol therapy and remain in first complete remission.**

****As measured by radiograph of the wrist or other bone per institutional standards.**

7.2 Research Studies for which Patient Participation is Optional

Standard Risk Ph+ ALL

Correlative Study	Diagnosis	Induction IA	Delayed Intensification[#]	Maintenance	Day +168 of Maintenance	End of Therapy
MRD (Section 14.2)		X				
BCR/ABL1 fusion variant (p190/p210) (Section 14.3)	X*	X	X	X	X	X
IKZF1 Deletions (Section 14.3)	X*					

[#] For patients assigned to Arm A (EsPhALL Arm): Obtain prior to Delayed Intensification #1

High Risk Ph+ ALL

Correlative Study	Diagnosis	Induction IA	Pre-Transplant	Day +56 Post-HSCT	Day +180 Post-HSCT	Day +365 Post-HSCT
MRD (Section 14.2)		X	X	X	X	X
BCR/ABL1 fusion variant (p190/p210) (Section 14.3)	X*	X	X	X	X	X
IKZF1 Deletions (Section 14.3)	X*					

***Note:** **Do not** monitor MRD with *BCR/ABL1* fusion variant (p190/p210). Please refer to Section 14.3 for details.

8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Resistant disease, defined as follows:
   - MRD $\geq 10^{-2}$ assessed by IgH-TCR-PCR (or MRD $\geq$ 1% if assessed by flow cytometry) or morphologic residual disease (M2 marrow confirmed by flow cytometry, *BCR-ABL1* FISH or IgH-TCR PCR; or M3 marrow) at the end of Consolidation Block 3 (HR patients)

b) Relapse (See Section 3.3 for definition)
c) Progressive disease post-HSCT (HR patients): MRD $\geq 10^{-2}$ if assessed by IgH-TCR-PCR (or MRD $\geq$ 1% if assessed by flow cytometry) at two post-HSCT time points separated by at least 2 weeks.
d) Refusal of further protocol therapy by patient/parent/guardian.
e) SR patients who decline randomization.
f) HR patients who receive any other chemotherapy pre-HSCT other than treatment specified in the protocol.
g) Completion of planned therapy.
h) Physician determines it is in patient's best interest.
i) Development of a second malignancy.
j) Pregnancy

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Withdrawal of consent for any further data submission.
d) Tenth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

9.1.1 Primary Endpoint

To compare disease free survival (DFS) of SR pediatric Ph+ ALL patients treated with continuous imatinib combined with either a high-risk COG-ALL chemotherapy backbone or the more intensive EsPhALL chemotherapy backbone. The primary endpoint, DFS, is defined as the time from randomization to first event (relapse, second malignancy, or death in complete remission) or time to last follow-up for patients without events. DFS comparison will be done according to the intention to treat (ITT) principle by assigned arm.

9.1.2 Secondary Endpoints

9.1.2.1 To determine the feasibility of administration of imatinib after allogeneic HSCT in HR Ph+ ALL patients

9.1.2.2 To determine event free survival (EFS) of HR pediatric Ph+ ALL patients treated with EsPhALL chemotherapy, HSCT in first complete remission and post-HSCT imatinib. EFS is defined as the time from the date of bone marrow for MRD assessment at end-IB to first event [resistant disease (MRD $\geq$ 10-2 or morphologic residual disease at end of Consolidation Block 3), relapse, progressive disease (i.e. MRD $\geq$ 10-2 at two post-HSCT time points separated by at least 2 weeks obtained at Day 90 or later from HSCT), second malignancy, or death in complete remission] or time to last follow-up for patients without events.

9.1.2.3 To compare rates of Grade 3 or higher infections in Standard Risk Ph+ ALL patients between the two randomized arms.

9.1.2.4 To evaluate EFS and overall survival (OS) of all eligible Ph+ ALL patients enrolled on the study.

9.1.2.5 To evaluate OS in SR patients. OS as secondary endpoint is defined as the time from randomization to death from any cause.

9.1.2.6 To evaluate OS (defined as time from MRD assessment at end-IB to death from any cause) in HR patients.

9.1.3 Exploratory Objectives

9.1.3.1.To describe toxicities associated with post-HSCT administration of imatinib.

9.1.3.2 To evaluate long-term toxicities in SR patients treated with chemotherapy plus imatinib (no transplant) overall and between randomized arms.

9.1.3.3 To determine prognostic significance of MRD in Ph+ ALL at various time points during therapy.

a. To determine the prognostic significance of MRD at end of Induction IA.

b.. To evaluate MRD in HR patients just prior to HSCT and then at regular intervals post-HSCT and explore the association of these measurements with long-term outcome.

c. To evaluate concordance of MRD assessments made by IGH-TCR PCR assay and Next Generation Sequencing (NGS) assay.

9.1.3.4 To determine prognostic significance of IKZF1 gene aberrations and deletions.

9.1.3.5 To determine frequency and prognostic significance of p190 and p210 BCR-ABL1 fusion variants in pediatric Ph+ ALL.

9.1.3.6 To measure adherence to oral chemotherapeutic agents (imatinib, 6-mercaptopurine and methotrexate) for 6 months during the maintenance phase in Standard Risk Ph+ ALL patients.

a.To identify factors associated with poor adherence.

b.To determine association between relapse risk and adherence to each oral chemotherapeutic agent (separately and combined).

9.1.3.7 To measure adherence to imatinib after allogeneic HSCT in High Risk Ph+ ALL patients and identify factors associated with poor adherence.

9.2 Patient Accrual and Expected Duration of Trial

Patients will be stratified based on End IB MRD into SR (MRD $<5 \times 10^{-4}$) and HR (MRD $\geq 5 \times 10^{-4}$); see Section 4.1.

The trial will enroll a maximum of 700 subjects at COG and EsPhALL sites (approximately 120 per year) Based on results of the ongoing EsPhALL and recently completed AALL1122 trials, it is assumed that 80-85% of enrolled patients will be found to have low MRD at the end of the Induction IB phase and will be considered SR according to the definition above, and the remaining 15-20% will classify as HR. Accounting for refusal to randomization (SR patients) and those unable to proceed to HSCT and/or seeking alternative therapies (HR patients), we anticipate 700 total enrolled subjects being sufficient to reach the target of 475 eligible, evaluable and randomized SR patients and 90-120 HR patients receiving post-HSCT imatinib. Accrual will close upon enrolling 475 randomized SR patients.

Randomization:
Consenting SR patients will be randomized to Arm A (EsPhALL Arm) or Arm B (Investigational COG Arm), with stratification balancing accrual for study group [COG and EsPhALL].

9.3 Statistical Analysis Methods

The primary analyses for the study will include data on patients from all participating sites in Europe and North America.

For the primary endpoint, we will use a non-inferiority design in order to evaluate whether there is significant erosion in DFS in SR Ph+ ALL patients treated with the less intensive chemotherapy backbone (Arm B) compared with the EsPhALL backbone (Arm

A). For the purpose of power calculations, based on previous trials conducted by COG and EsPhALL groups using TKI + chemotherapy to treat Ph+ ALL, we estimate that the baseline 3-year DFS for SR patients treated on the EsPhALL arm (Arm A) will be 70%. This value was based on the 3-year DFS for Good Risk patients in the recently completed amended EsPhALL trial that used this backbone plus imatinib. We define the non-inferiority margin to be a hazard ratio of 1.43, which corresponds to the investigational Arm B having 60% 3-year DFS. Thus, the study has the alternative hypothesis of non-inferiority, which is accepted if the upper bound of the one-sided 95% hazard ratio confidence interval is less than or equal to 1.43. Otherwise, the null hypothesis of inferiority of the investigational Arm B is not rejected and the study cannot conclude that there is non-inferiority. The study is powered under the alternative assumption of equivalence between the arms (hazard ratio=1) and assumes 6 years of accrual time and 3 years of minimum follow-up. Based on decreasing hazard rates found in event distributions from the recently completed amended EsPhALL trial, and similar to the rates from AALL0031 and AALL0622, we are assuming a failure rate model based on a Weibull distribution with a shape parameter of 0.58. With these assumptions, n=475 randomized patients (with 194 events) would be needed for 80% power[77].

Methods of analysis:
EFS, DFS and overall survival (OS) will be estimated using the Kaplan-Meier method and standard errors estimated by Greenwood. Estimation of treatment effect in randomized SR patients (ITT analysis) will be done on DFS calculating the hazard ratio and its one-sided 95% confidence interval adjusting by study group in a Cox model, after checking the proportional hazards assumption.

Interim analysis plan:

DFS Comparison of Randomized Arms (SR patients):
Interim monitoring for futility will take place at the study year time when approximately 1/4, 1/2, and 3/4 of expected events have occurred. The futility boundaries are based on repeated testing the alternative hypothesis at the 0.039 level.[78,79] That is, if the one sided log rank test at the 1/4, 1/2, or 3/4 information mark shows evidence of a hazard ratio > 1.0 (alpha<0.039 or Z>1.76), we would stop and conclude that there is evidence of inferiority of the investigational Arm B. This alpha level corresponds to that which would cause futility stopping at hazard ratio estimate of 1.43 when 50% of required events are observed, assuming an n of 475 SR randomized is obtained. [78] This is the number that would give 80% power for the primary non-inferiority test, with 194 events expected. In this case, the stopping bounds approximately correspond to estimated hazard ratios of 1.66 at the first interim point (after 48 events), 1.43 at the second interim point, and 1.34 at the final interim point (after 145 events). Simulation results with 10,000 study replications have shown that this monitoring plan will cause a small loss of power (2.0%) for the final test below those shown above.

Additionally, to prospectively guard against the possibility that the long-term event rates are lower than those used in the design power/sample size calculation, we will conduct the following monitoring plan. After approximately 50 and 100 EsPhALL Arm A patients have been followed for 3 years the model assumptions used in the sample-size calculation will be re-evaluated. If needed, possible changes to the design / sample-size will be considered. If under the observed event rate, the feasible design adjustments

cannot keep the study power above 70%, then the rationale for continuing the study will be reexamined.

*Feasibility of Post-HSCT imatinib in HR patients (**Secondary Endpoint 1**)*
We define feasibility of post-HSCT imatinib based on the proportion of patients who receive at least 75% of intended doses. Patients who electively stop imatinib early for any reason or experience a treatment-related death during the post-HSCT observation period would be considered "failures" when assessing feasibility of post-HSCT imatinib administration. Patients who stop imatinib early due to relapse will not be considered "failures" for feasibility analysis. Such patients will not be considered evaluable for the feasibility endpoint and will be removed from both the numerator and denominator of the feasibility success proportion. Ad hoc analysis will also be done, considering any relapses during post-HSCT imatinib treatment as feasibility "failures" to explore any differences in conclusions.

Assuming that 15-20% of patients will be HR and accounting for patients who do not proceed to HSCT, seek alternative therapies, and/or decline post-HSCT imatinib, we expect 90-120 patients to be in the HR arm and to receive post-HSCT imatinib. This will allow a maximum (conservative) standard error for the estimated proportion of 5.3% (for 90 patients). The study will enroll no more than 120 HR patients to the post-HSCT imatinib group. With n=90, and a true 'feasibility success' proportion of 0.82, the study would have 82% power to reject the null hypothesis of p=0.7 using an exact one-sided binomial test with alpha=0.05. With n=120, the study would have 92% power under the above conditions, but would still have 79% power to reject if the true proportion was 0.80. Additionally, an interim analysis for low feasibility will be performed. When n=45 HR patients are evaluable for dosing success, if the number of successes is ≤ 31 (out of 45), then we will claim that feasibility cannot be confirmed. For true rates of 60%, 70%, and 80% we would have 0.92, 0.49, and 0.05 probability of stopping in this scenario.

DFS for HR patients (***Secondary Endpoint 2***):
Three year EFS will be estimated for HR pediatric Ph+ ALL patients treated with EsPhALL chemotherapy, HSCT in first complete remission and post-HSCT imatinib. It is projected that 90-120 HR patients will receive the combination therapy. The 3-year EFS for these patients will be estimated with a maximum standard error of 5.3%.

*Toxicity Comparison of Randomized Arms (SR patients) (**Secondary Endpoint 3**)*
Monitoring of toxicity will focus on severe infections (Grade 3 or higher, according to CTCAE, Version 4.0) observed during the randomized phases and therefore we will compare the rate of infections during the post IB/pre-maintenance phases of treatment accounting for follow-up time. The rate of severe infections during the three Consolidation Blocks observed in SR patients treated with the amended EsPhALL protocol (Arm A) was 28/94=0.30. The table below shows the power calculations for toxicity rate comparison between the randomized arms at the n=475 eligible and evaluable target sample size, taking into account different scenarios in terms of baseline rate and rate in investigational arm. Calculations are based on the two-sample, one-sided Poisson test (12) with type-one error alpha=5%.

# Randomized SR patients	Baseline toxicity rate	Investigational Arm B toxicity rate	Absolute reduction from baseline	Power (alpha=5%; one-sided test)
475	*0.25*	*0.17*	*0.08*	*78.6%*
475	*0.30*	*0.21*	*0.09*	*79.5%*
475	*0.35*	*0.25*	*0.10*	*80.6%*

A two-sample Poisson test would have ~80% power to detect a 30% reduction in the severe infections rate of the experimental treatment (investigational Arm B) from a baseline of 0.30 in the standard treatment (EsPhALL Arm A, type-one error alpha=5%, one-sided test).

Overall EFS and OS (***Secondary Endpoint 4***):

The EFS and OS rates will be estimated for all eligible patients on study. Here, EFS is defined as time from enrollment until the first occurrence of: M3 marrow at the end of Induction IA, relapse, second malignancy, or death as a first event. OS is defined as the time from study enrollment to death from any cause. Patients who are event-free will be censored at the time of last follow-up. Assuming a 5% ineligibility rate would give approximately n=665 patients for this analysis. Under this assumption, the 3 year overall EFS and OS rates could be estimated with a maximum standard error of 1.9%.

OS for SR patients (***Secondary Endpoint 5***):
OS (the time from randomization to death from any cause) will be estimated for SR patients. Patients who are alive will be censored as of the date of last follow up. With n=475 patients enrolled on the SR group, the OS rate can be estimated with a maximum standard error of 2.3%. OS rate estimates will also be calculated for each of the randomization groups: standard Arm A and investigational Arm B (maximum standard error of 3.2% in each group). The study is not powered to detect any differences between these rates, but they will be described.

OS for HR patients (***Secondary Endpoint 6***):
OS (the time from the date of MRD assessment at end-IB to death from any cause) will be estimated for HR pediatric Ph+ ALL patients treated with EsPhALL chemotherapy, Patients who are alive will be censored as of the date of last follow up. HSCT in first complete remission and post-HSCT imatinib. It is projected that 90-120 HR patients will receive the combination therapy. The 3-year OS rate for these patients will be estimated with a maximum standard error of 5.3%.

*Toxicities of HR patients treated with post-HSCT imatinib (**Exploratory Objective 1**):*
Frequencies of target toxicities in HR patients after the initiation of post-HSCT imatinib through Day +365 will be described and presented to the DSMC at regular intervals. Unusually high toxicity rates will result in discussion about potential changes to the post-HSCT imatinib treatment plan for the study. For the HR patients, the specific targeted toxicities will include Grade 4 neutropenia, Grade 4 thrombocytopenia, Grade 3 or higher bilirubin, Grade 4 or higher transaminitis, Grade 3 abdominal pain, Grade 3 nausea, Grade 3 or higher diarrhea, Grade 3 edema (limbs and trunk), Grade 3 myalgia, Grade 3 maculopapular rash, Grade 3 fatigue, Grade 3 headache, Grade 3 or higher hyposphosphatemia, and Grade 3 or higher infection.

*Long-term toxicities in SR patients (**Exploratory Objective 2**):*
Frequencies of long-term toxicities associated in patients treated with chemotherapy and imatinib (no transplant) will be described and differences between randomized arms will be explored. Specific long-term toxicities to be explored include cardiac (echocardiographic abnormalities, including decreased LV function and decreased LV wall thickness), growth (linear height, bone age), and second malignant neoplasm.

Prognostic significance of MRD (***Exploratory Objective 3***):
For both SR and HR risk groups, frequencies and prognostic significance (DFS, EFS, OS) will be explored for MRD levels at end of Induction IA (i.e. MRD negative, detectable at $< 5 \times 10^{-4}$, and dectectable at $\geq 5 \times 10^{-4}$).. Additional MRD measurement and analyses will be conducted as described below.

MRD Analysis in HR
The outcome of HR patients will be described, including proportion of patients who achieve MRD-negativity just prior to HSCT, and at regular intervals post-HSCT. Associations between these findings and long-term outcomes (e.g., OS, DFS) will be explored.

MRD by IGH-TCR PCR and Next Generation Sequencing (NGS) assays

Concordance of MRD assessments made by IGH-TCR PCR assay and Next Generation Sequencing (NGS) assay will be described and evaluated. All COG patients who consent to research samples will have both assay types completed. Scatter plots and diagrams will be used to examine agreements and patterns of agreement or any differences found.[80] Concordance will be explored both for the overall cohort, as well as by risk group. The increased sensitivity of the NGS will be closely examined to find cases where the MRD levels are detectable by NGS but undetectable by PCR, as well as cases in which one test yields results and the other does not (test failure). Prognostic relationships on outcomes for these subjects will be inspected.

*Prognostic significance of IKZF1 and p210 BCR-ABL1 (**Exploratory Objectives 4 and 5**):*
For both SR and HR risk groups, frequencies and prognostic significance (OS, DFS) will be explored *IKZF1* gene aberrations and deletions, and p190 versus p210 *BCR-ABL1* fusion variants.[81]

Adherence Monitoring (***Exploratory Objectives 6 and 7***):
The adherence component of AALL1631 will be open to participants enrolled at COG sites, and will be led by Dr. Smita Bhatia who conducted previous COG adherence studies in ALL patients. Adherence to imatinib, 6-mercaptopurine and methotrexate will be evaluated in COG-enrolled participants using an electronic monitoring device (MEMS: Westrock Switzerland Ltd, Switzerland). The MEMS cap uses microelectronic technology to record date and time of each pill bottle opening.

Adherence rate for imatinib, 6MP and methotrexate will be defined as the ratio of the number of days with MEMS cap openings (X) to the number of days imatinib, 6MP or

methotrexate was prescribed (N), reported as a percentage (X/N*100). Days when imatinib, 6MP or methotrexate was withheld by the prescriber will be removed from the denominator (N). Adherence rate will be computed for each month of adherence monitoring. Longitudinal binomial regression will be conducted using generalized estimating equation methods by modeling monthly adherence rate as an unstructured mean model using five indicator variables of time for the study months. Time in months will also be treated as a continuous variable to explore temporal trends in adherence rate. Compound symmetry will be assumed as the working correlation matrix over time. Covariates that will be considered for adjustment include those hypothesized to be predictors of adherence (sex, age at study participation, race/ethnicity, social structure (availability of adult caregivers), annual household income, parental education, time since start of maintenance, risk classification for ALL, and imatinib, 6MP and methotrexate dose-intensity.

Sample size and power calculations for adherence: Non-adherence will be defined as taking <95% of prescribed doses according to the MEMS. For SR patients, we assume that we will have a sample size of 200 evaluable patients treated at COG institutions entering into maintenance in 1st CR, with an expected non-adherence rate of 40%. With this sample size, and an assumed overall participant event rate of 40% (based on hazard rate assumptions above), we will have 80% power to detect a hazard ratio of relapse of 1.76 between non-adherers and adherers with a one-sided test at alpha=0.05. For HR patients, we expect 60 patients to participate in the post-HCT adherence study (from US). We define feasibility of measuring post-HSCT imatinib adherence as the ability to have ~75% of the 60 (n=45) complete the adherence assessment from Day +56 to Day +100. Frequency of non-adherence will be described, and factors related to non-adherence will be explored.

The primary and secondary analyses for the study will include data on patients from all participating sites in the EsPhALL network and North America.

9.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

The below accrual is for COG sites. The remaining accrual will be from EsPhALL sites, for which historical data onrace/ethnicity is not available.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	7	1	1	**11**
Asian	7	7	1	1	**11**
Native Hawaiian or Other Pacific Islander	1	4	1	0	**6**
Black or African American	9	27	4	4	**44**
White	48	154	21	22	**245**
More Than One Race	0	0	0	0	**0**
Total	**62**	**199**	**28**	**28**	**317**

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	4	2	0	0	**6**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	2	0	0	**6**
White	14	7	0	0	**21**
More Than One Race	0	0	0	0	**0**
Total	**22**	**11**	**0**	**0**	**33**

This distribution was derived from the observed distribution from COG protocol AALL0622.

10 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. Toxicities are to be reported on the appropriate case report forms.

10.2 Response Criteria for Patients with Leukemia

See definitions in Section 3.3

11 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

11.2 Determination of Reporting Requirements

Definitions:

An Adverse Event (AE) is any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational medicinal product (IMP). An AE can therefore be any unfavorable and unintended sign (e.g. any abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical product, whether or not a causal relationship (i.e. related/not related) with the treatment is suspected.

An Adverse Reaction (AR) is any untoward and unintended response to an IMP related to any dose administered. In general, a reasonable causal relationship is established when it is supported by evidence or argument, i.e. the SAE is potentially related to a study drug.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- is fatal (results in death)
- is life-threatening (that is, when patient was at substantial risk of dying at the time of the adverse event; it does not refer to an event that, had it occurred in a more severe form, might have caused death)
- requires or prolongs in-patient hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant (defined as any clinical event or laboratory result that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention, to prevent one of the other serious outcomes listed in the definition above).

A Serious Adverse Reaction (SAR) is a SAE judged as having a reasonable causal relationship to a medicinal product as defined above.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a SAR that is unexpected i.e. the nature or severity of the event is not consistent with the applicable product information, such as drug monograph, Summary of Product Characteristics (SmPC) or Investigator Brochure (IB).

Reporting Requirements:

Assessment of both causality (suspected/not suspected relationship with the study drugs) and expectedness (expected/not expected) is needed for any SAE. Assessment of causality has to be done by the reporting clinician/investigator in the SAE CRF (see Section 1.4), which is sent via the web-EsPhALL trial database to the National Trial Unit

for re-assessment of causality and assessment of expectedness according to the pre-specified drug information documents listed above, as appropriate. After the assessment, the National Trial Unit forwards the SAE CRF to the Central Pharmacovigilance Unit of the Sponsor via the trial database. The Central Pharmacovigilance Unit will assess the SAE received in terms of seriousness, severity (NCI-CTCAE v4.0), causality (i.e. relationship to the study drugs) and expectedness.

In case of a SUSAR, the Central Pharmacovigilance Unit will report the event in the EMA EudraVigilance database, through EVWEB, according to EU legislation. The CIOMS form obtained from EVWEB will be sent by the Central Pharmacovigilance Unit to each National Trial Unit, which is responsible for the reporting in its own country, i.e. to investigators, national ethics committee(s, ECs) and national competent authority (CA), as required by national legislation. In particular, SUSARS which are fatal or life threatening are to be communicated within 7 days (and detailed follow-up information within additional 8 days). All other events categorized as SUSARs are to be reported within 15 days.

The Central Pharmacovigilance Unit will report details of all SARs (including SUSARs) in an annual Development Safety Update Report (DSUR). The DSUR will be sent to National Trial Units that will take care of forwarding it to national EC(s) and national CA, as required by national legislation.

Reporting requirements for AEs and SAEs are detailed in the Section 11.4 below.

Secondary Malignancy

> A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy. All secondary malignancies that occur following treatment need to be reported.

Second Malignancy

> A ***second malignancy*** is one unrelated to the treatment of a prior malignancy. All second malignancies that occur following treatment need to be reported.

11.3 Reporting of Adverse Events for Commercial Agents– via CTEP-AERS

This Section applies only to COG centers.

11.4 Adverse Event Reporting

Adverse Events

All AEs will be described and graded according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Investigators must report all AEs with the AE protocol CRF via the web-EsPhALL trial database. Should any seriousness criterion be met, the event is to be reported with the SAE protocol CRF.

The following AEs, considered medically relevant, are to be reported:

- all non-hematologic toxicities which resulted in the death of the patient (grade 5) or meet the definition of SUSAR above
- all grade ≥4 AEs
- the following grade <4 AEs:
  1. CNS hemorrhage requiring medical intervention (Grade 2 or 3)
  2. GI bleed requiring operative or interventional radiology intervention (Grade 3)
  3. Pancreatitis requiring medical intervention (Grade 2 or 3)
  4. Osteonecrosis interfering with function (Grade 2 or 3)
  5. Transient ischemic attacks (All grades)
  6. Stroke (All grades)
  7. Encephalopathy (Grade 3)
  8. Neuropathy; motor or sensory, interfering with ADL (Grade 3)
  9. Seizure (Grade 2 or 3)
  10. Allergic reaction (Grade 3)
  11 Ileus (Grade 3)
  12. Mucositis/stomatitis; functional (Grade 3)
  13. Bilirubin (Grade 3)
  14. Thrombosis (Grade 3)
  15 Infections (grade ≥3, exceptions apply, see below).

Diagnosis of grade ≥3 infection requires an identified source (such as positive culture from blood or other tissue/fluid, other positive test result for bacterial, fungal, viral or other infectious etiology, radiographic finding or physical exam finding consistent with infection). Episodes of fever without any identified source are excluded as infectious events.
Severity of peripheral motor and sensory neuropathy will be additionally graded with the Balis scale (see Section 5.14).

For HR patients only, the following toxicities will also be collected during post-HSCT treatment with imatinib: Grade 4 neutropenia, Grade 4 thrombocytopenia, Grade 4 or higher transaminitis, Grade 3 abdominal pain, Grade 3 nausea, Grade 3 or higher diarrhea, Grade 3 edema (limbs and/or trunk), Grade 3 myalgia, Grade 3 maculopapular rash, Grade 3 fatigue, Grade 3 headache, Grade 3 or higher hypophosphatemia.

Serious Adverse Events
Any SAE which comes to the attention of the investigator at any time during the study since consent is given and within 30 days after the last administration of any study drug, independent of the circumstances or suspected cause, must be reported immediately, within 24 hours of learning of its occurrence (on the next working day at the latest). Any event which is considered to be possibly or probably related to trial treatment and occurring after these time periods, should be reported, regardless of time elapsed since last study drug dose. Events exclusively related to tumor relapse or progression progressions are not considered as SAE.
Investigators must report the SAEs with the SAE CRF via the web-EsPhALL database. The database will automatically notify the National Trial Unit to permit the assessment of causality and expectedness as described above. After ensuring that the SAE Form is accurately and fully completed, the National Trial Unit submits the SAE CRF into the trial database which will automatically alert the Central Pharmacovigilance Unit for final review of seriousness, severity, causality and expectedness of the event. Any relevant

follow-up information about a reported SAE must also be reported timely with the same modalities.
The investigator shall supply the Central Pharmacovigilance Unit, the National Trial Unit, the EC(s) and the national CA with any additionally requested information, as appropriate.

Exceptions: The following events are not to be considered as SAEs (please note that examples listed below do not cover all possible clinical events, but are the most common adverse events not to be reported as serious):

- Hospitalization occurring under the following circumstances:
  a) planned as per protocol medical/surgical procedure
  b) admission for medical events that, according to medical and scientific judgement, are neither immediately nor hypothetically life-threatening
  c) routine health assessment requiring admission for baseline/trending of health status documentation
  d) medical/surgical admission for purpose other than remedying ill health state (planned prior to entry into study trial)
  e) admission encountered for other life circumstance that carries no bearing on health status and requires no medical/surgical intervention (i.e. lack of housing, economic inadequacy, care-giver respite, family or administrative circumstances)
- Hospitalization due to/for
  a) neutropenic fever without clinical signs or imaging showing or suggestive for infection
  b) uncomplicated drug-induced diabetes mellitus (except if requiring insulin treatment longer than 1 week),
  c) uncomplicated impaired MTX excretion (except cases with MTX level of > 10 μmol/l at h 36 and/or > 5 μmol/l at h 42 and/or > 3 μmol/l at h 48),
  d) parenteral nutrition or i.v.-rehydration due to mucositis, inappetence/ anorexia or vomiting/diarrhea.

Hence, hospitalization due to adverse events which
- are common side effects of the administered drugs according to the SmPC *and*
-do not meet other seriousness criteria (i.e., death, life-threatening consequences, significant disability/incapacity, congenital anomaly/birth defect, medically significance) *and*
- are not included in the list of medically relevant AEs listed above,

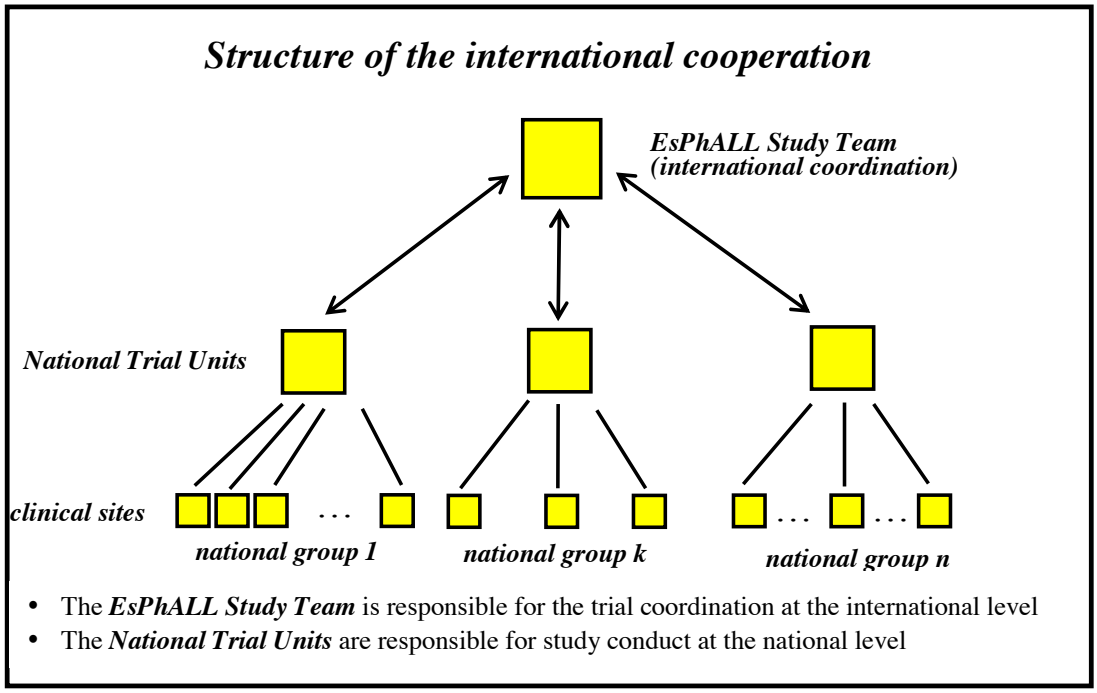
is not to be considered as SAE.

12 RECORDS AND REPORTING

Structure of the international cooperation and data collection

Each participating group will refer to the National Contact Person, the National Trial Unit (including the data centre, trial coordinators, statisticians, biologists, etc.) and the national network of clinical centres for the conduct of this protocol, the monitoring of data collection and data quality and to activate the randomization procedure. The EsPhALL Study Chair and Vice-Chair, the Study Statistician, the staff of the EsPhALL Study Coordination and Data Center, the Clinical Coordination and the Central Pharmacovigilance Unit will be members of the EsPhALL Study Team. The EsPhALL Study Team will act as a trial coordination unit at the international level, for the monitoring and exchange of information and for the pooling of the data. Contact details of the components of the EsPhALL Study Team can be found on page 15. The EsPhALL

Study Team will work in co-operation with the EsPhALL Study Steering Committee (composed by the Study Chair and the Study Vice-Chair and by all National Contact Persons) to ensure a smooth data collection process.



See contact details of the EsPhALL Study Team and the National Trial Units at the beginning of the protocol.

The data collection within the EsPhALL network is based upon:

- registration of each new Ph+ ALL according to flow chart in Section 3.1.
- a common study database, accessible on the internet at https://web-esphall.trialcenter-unimib.org. Data of each Ph+ ALL patient who enter the study screening will be saved in this database.
- Randomization (for SR patients) will be performed through a rountine available in the study database.

Paper Case Report Forms (CRFs) will be provided by the EsPhALL Study Team to each National Trial Unit, which will distribute them together with the relevant protocol documents to the authorized sites. Paper CRFs give an overview of data required for each patient. Sites are requested to enter data directly into the web-EsPhALL database at https://web-esphall.trialcenter-unimib.org. CRFs may be amended by the EsPhALL Study Team, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, participating sites will be promptly notified of the new CRFs and consequent changes in the database.

In summary, for what concerns data collection, each national participating group is required to:

- enter patients' data in the common web-EsPhALL database at https://web-esphall.trialcenter-unimib.org;
- instruct personnel at each clinical site about data collection and provide training for the use of the web-EsPhALL database (the EsPhALL Study Team will provide supporting materials). Each authorized clinical site will receive credentials to access the database;
- keep its own data in the web-EsPhALL database updated and provide periodic update of follow-up as requested (see below). Each National Trial Unit will be able to extract its own data from the database.

More specifically, each participating investigator/institutionis required to:

1. register at https://web-esphall.trialcenter-unimib.org each new Ph+ALL, regardless of whether this patient will subsequently enter the EsPhALL2007/COGAALL1631 protocol. This is necessary in order to know which percentage of eligible patients is treated according to the protocol. Registration should be done timely according to flow chart in Section 3.1;
2. report immediately each event (as defined in Section 9.1) in the web-EsPhALL database;
3. report each SAE to the National Contact Person and Trial Unit via the web-EsPhALL database, within 24 hours from learning of its occurrence;
4. save in the web-EsPhALL database, on a regular basis, the CRFs on diagnosis, response, randomization (for SR patients), treatment and toxicity, as soon as they can be completed. Please consider that randomization can be obtained directly from the web-EsPhALL database only if registration, eligibility, diagnosis and MRD data at end-IB are available.
5. up-date the follow-up every 6 months for the first 5 years after enrollment and then annually until end of trial included. At least at the beginning of each new calender year (or as requested by the EsPhALL Study Team) data must be updated and frozen with follow-up updated at December of the previous year.

For eligible Ph+ALL registered but not enrolled in the protocol, follow-up data only might be routinely requested.

Progress reports will be produced by the Study Coordination and Data Center and the Study Statistician. Periodicity and contents (e.g. information on recruitment, analyses, including interim analyses, etc.) will be according to protocol and DSMC charter, as appropriate.

The study data and the EsPhALL web-database

The EsPhALL Study Team, in collaboration with the Study Chair and the National Trial Units will be responsible for maintaining the study database at https://web-esphall.trialcenter-unimib.org and evaluating the data according to protocol aims.

Access to the common web-EsPhALL database will be granted on the Internet to the clinical sites, the National Contact Persons and Trial Unitsof each participating group, as well as to the staff of the EsPhALL Study Team, with different modalities. For this purpose, the web-site will be designed by the EsPhALL Study Data Center in collaboration with the IT staff at CINECA (Consorzio Interuniversitario per il Calcolo Automatico, Bologna, Italy). The web-site will provide the interface for data input and modification (electronic CRFs will reflect the paper CRFs), the archive of the protocol documents and a forum for communication among participating groups.

The web-site is implemented in such a way that data confidentiality and data security standards are met. In particular, data confidentiality is ensured by:

- Separation of demography data from sensitive patient data. Only demography data pertinent to the study are collected (and in an anonymous form whenever possible).
- Data traffic with the server is encrypted with high grade of cryptography (up to 128 bit) and X.509 Certificate (SSL).
- Access to web-site is only possible through valid user identification (i.e. USERID) and associated password. Users may change his/her password at any time.

Data security is ensured by:

- Controlled access to the server data (see above).
- Appropriate daily backup of all data on electronic media, to allow restoration in case of loss or damage of the database. Protection against major disasters (fire, flooding, etc.) and Disaster Recovery Procedures are implemented.
- Operation tracking log (registration of any operation by any user) and electronic data audit trials (creation of a database of original entries/modifications with identification of date, time, source and user identity).

Property of data and rights to the use of study results are defined in a written agreement between the coordinating international sponsor (the University of Milano-Bicocca) and the National sub-sponsors ('Agreement for the delegation of sponsor obligations'). Trial data will be used under the international sponsor and sub-sponsors responsibility for the trial aims, and will be communicated to CAs and ECs by the international sponsor and the sub-sponsors as appropriate according to the agreement metioned above and applicable laws. Terms of confidentiality and publication of results are also set in this agreement.

Quality Management

As required by the Guidelines for Good Clinical Practice of the International Council for Harmonisation, (ICH-GCP) section 6.10 and according to the contract between the coordinating sponsor and the national sub-sponsors, the participating investigators/institutions will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

Site Set-up and Initiation

All participating investigators/institutions should maintain the "Site Signature and Delegation Log" with the list of all qualified and trained persons in the study staff and description of study-specific roles and responsibilities assigned to each of them. All members of the site study staff will be required to sign the "Site Signature and Delegation Log" which should be returned to the National sub-sponsor.

Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site study staff will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File.

On-site Monitoring

The study will be carried out in compliance with international and national regulations and according to quality and conduct standard procedures of the participating national sub-sponsor. Such procedures must be compliant with ICH-GCP and all national and international regulations (e.g. Directive 2001/20/EC as subsequently modified/substituted by EU Regulation 536/2014).

The national sub-sponsors are responsible for the organization of an adequate monitoring process in the respective country and for reporting about this activity to the Sponsor (EsPhALL Study Team). At least one on-site monitoring per site will be conducted. In case of frequent protocol violations, incomplete documentation, unanswered queries or other problems, additional monitoring visits may be performed. On-site monitoring visits aim at ensuring that the study is performed according to ICH-GCP, and that the protocol is adhered to. In particular, focus will be on the informed consent forms, the compliance with inclusion and exclusion criteria as well as on the main efficacy and safety endpoints.
In order to arrange a visit, the National sub-sponsor will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the trial staff of the National sub-sponsor access to source documents as requested.

Central Monitoring
The National Trial Unit appointed by the National sub-sponsor will be in regular contact with each site study staff to check on progress and address any queries that they may have. The National Trial Unit staff in co-operation with the EsPhALL Study Team will check data received for compliance with the protocol, data consistency, missing data and timing. Sites will be sent requests regarding missing data or clarification of inconsistencies or discrepancies.
Sites may be suspended from further recruitment in the event of serious and persistent noncompliance with the protocol and/or ICH-GCP guidelines. Any major problems identified during monitoring may be reported to the Trial Steering Committee and the relevant regulatory bodies. This includes reporting serious breaches of ICH-GCP and/or the trial protocol to the EC(s) and CA(s).

Audit and Inspection
The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. Sites are also requested to notify the National sub-sponsor of any CA inspections.

Archiving
It is the responsibility of the Principal Investigator at each site to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 5 years after the end of the trial (and according to national laws). Do not destroy any documents without prior approval from the National sub-sponsor.

End Of Trial Definition
The trial aims at recruiting patients for 6 years and the minimum follow-up requested is 3 years. Considering this and in order to allow sufficient time for the completion of protocol procedures, data collection and data checks, the end of trial will be 6 months after the last patient has completed trial procedures as per protocol (including studies at 3-year post end of therapy).

Ethical, Legal And Regulatory Aspects And Agreements

Ethical considerations
The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, whose principles that have their origin in the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html).

Moreover, the trial will be conducted in accordance with the relevant legislation in each participating nation state and the ICH-GCP.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain all applicable regulatory approval(s). Sites will not be permitted to enroll patients until written confirmation of such approval(s) have been received by the National sub-sponsor.

It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments, if any, gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

Patient information and informed consent
Before enrolment, the Principal Investigator at each site (or his/her delegate as per Site Signature and Delegation Log), will make sure that each patient receive full oral and written information about the nature, purpose, anticipated benefits and potential hazards of the trial. The patient and his parents/legal guardians will agree to participation in the trial by signing the informed consent form. Patients and their parents must be given an opportunity to enquire details of the study. After a sufficient period of time for the individual's consideration and decision, comprehension and consent shall be documented on the consent form by the dated signature of the patients' parents, the patient, if applicable, and the investigator/ treating doctor. The parent(s) or a legal guardian must read, sign, and date the consent form before his or her child enters the trial, takes study treatment or undergoes any study-specific procedures. If the child is able to comprehend the study, and according to local policy/requirements, he/she may also sign an informed consent form. An example of the patient information form and the patient consent form is attached to this protocol. It is responsibility of each National sub-sponsor and participating site to adapt design and language to the local needs. The final versions of patient information and consent forms will be submitted to the EC. Both the patient information and the patient consent form are signed twice. One of each forms is for the patient file, another will be handed to the patient.

Confidentiality and data protection
Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the National Data Protection Laws. The Principal Investigator must maintain documents not for submission to the National sub-sponsor, (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the CAs, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected. The National sub-sponsor will maintain the confidentiality of all patient's data and will not disclose information by which patients may be identified to any third party, other than those directly involved in the treatment of the patient and organizations for which the patient has given explicit consent for data transfer (e.g. Cancer Registries, laboratory staff). Representatives of the trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

Patient insurance
Patient insurances are contracted by the national sub-sponsors (see 'Sponsorship' Section).

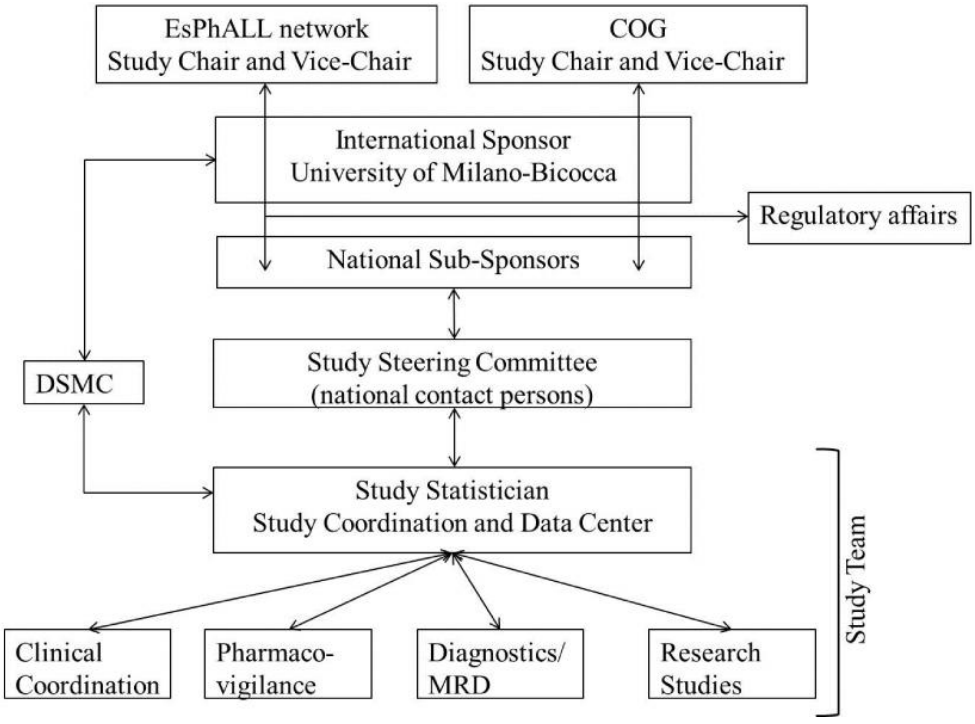
Sponsorship

The international sponsor for the trial is the University of Milano-Bicocca. The University of Milano-Bicocca intends to manage the conduct of the Study by appointing national (sub-) sponsors for local regulatory purposes in each nation state where the Study will be carried out, and providing centralized services to all national (sub) sponsors, with a view to enabling a coordinated collection and elaboration of data, statistics and results of the Study, as well as a comprehensive, worldwide clinical study report for the entire Study. Delegation of responsibilities and duties will be defined in a written agreement.

The Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Committee (DSMC) composed of experienced researchers not involved in the trial (including one statistician) will be responsible for providing the investigators with guidance on the trial conduct and for monitoring the progress of the study on ethic and scientific grounds. DSMC membership, terms of reference, responsibilities, decision-making etc. are described in the DSMC Charter in Appendix XVII.

Organization chart and cooperation between the EsPhALL network and COG



12.1 CDUS (Clinical Data Update System)

This Section applies only to COG.

13 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

No pathology review is planned for this study.

14 SPECIAL STUDIES REQUIREMENTS

14.1 Required Bone Marrow Sample and Shipping Information

The submission of a bone marrow sample for MRD probe development, and for MRD testing, is required at the following time points. Please submit samples as follows:

14.1.1 Bone Marrow for MRD Probe development and PCR Testing:

Submit a bone marrow sample at the following time points:

- Study entry collect a diagnostic bone marrow sample for MRD probe development.
- End of Induction IB (all patients, see Section 4.2.2)
- End of Consolidation Block #3 (High Risk patients only, see Section 4.21.2)

14.1.2 Bone marrow for Flow Cytometry MRD testing:

Specimens to be submitted:

- 5 mL of BM aspirate obtained prior to initiation of systemic anti-leukemia therapy is optimal.
- If an adequate marrow specimen cannot be aspirated, then a BM biopsy specimen may be substituted at the discretion of the cytogenetic laboratory; contact cytogenetic laboratory for questions regarding specimen handling.
- If an adequate marrow specimen cannot be aspirated, then PB may be substituted for BM if there are at least 1,000 circulating blasts/μL (i.e., a WBC count of 10,000/μL with 10% blasts or a WBC count of 5,000/μL with 20% blasts). If only PB is submitted, please obtain and send twice the volume of PB as the recommended BM volume specified in the tables. As long as there are at least 1,000/μL PB blasts, institutions are encouraged to submit PB in addition to BM samples to make sure that adequate material is available to perform the required studies.

14.2 Prognostic Significance of Minimal Residual Disease (MRD)

Timing of sampling

- End of Induction IA.
- Prior to HSCT
- Day +56 (start of post-HSCT imatinib therapy)
- Day +180 (6 months post-HSCT)
- Day +365 (12 months post-HSCT)

Sample Collection and Processing

Collect and ship bone marrow samples according to each national group policy.

- If samples cannot be shipped on the day of collection, please store at 4◦C until shipment on the next business day.

14.3 Diagnostic Bone Marrow Samples for the Minimal Residual Disease (MRD) Concordance Study between IgH-TCR PCR and Next Generation Sequencing, the *BCR-ABL1* fusion variant (p190 vs p210) Study, and the *IKZF1* Deletions Study.

For patients who gave consent, bone marrow and/or blood specimens should be submitted as per national group policy. At the time of diagnosis samples will be evaluated for the following:

- MRD Next Generation Sequencing to determine concordance with standard MRD IgH-TCR PCR methods.
- The prognostic significance of *BCR-ABL1* fusion variants (p190 vs p210) in Ph+ ALL.
- The prognostic significance of *IKZF1* gene aberrations and deletions in Ph+ ALL.

No additional samples are needed.

15 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

No imaging studies are planned for this study.

16 RADIATION THERAPY GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. 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 where explicitly prohibited within the protocol).

TOTAL BODY IRRADIATION (TBI): This study will not recommend any particular dose-fractionation regimen for TBI when indicated. The choice of the TBI regimen will be left to the treating institutions.

CRANIAL IRRADIATION: Cranial irradiation will be given to SR patients with CNS3 leukemia at diagnosis. It will be administered at the dose of 18 Gy in 10 fractions during either a) the first two weeks of the Interim Maintenance phase and completed by Day 14 (SR patients assigned to the EsPhALL arm (arm A), or b) the first 4 weeks of Maintenance therapy and should be completed by Day 29 (SR patients assigned to the Investigational COG Arm).

HR patients with CNS3 leukemia will not receive cranial irradiation during chemotherapy phases administered prior to preparative regimen for HSCT in CR1. It is recommended that HR patients going to HSCT who were CNS3 at diagnosis going to HSCT should receive a cranial boost prior to total body irradiation (TBI). If the TBI dose is 14 Gy TBI , a 4 Gy boost is recommended within two weeks of the preparative regimen. If TBI dose is 12 Gy, a higher boost (6 Gy) is recommended. If the myeloablative regimen does not include TBI, cranial irradiation (18 Gy) is recommended prior to the preparative regimen.

In the rare circumstance that an HR patient is unable to proceed to HSCT in CR1 and will continue to be treated per the HR chemotherapy arm (EsPhALl backbone), cranial irradiation should be administered during the first two weeks of the Interim Maintenance phase in HR patients with CNS3 disease at diagnosis.

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. 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 where explicitly prohibited within the protocol).

Radiation Therapy Guidelines

Equipment and Calibration: X-ray beams with a nominal energy of 4 or 6 MV. 3DCRT is required on this protocol for treatment of the cranial fields. IMRT is not allowed formally, but field-in-field and fluence optimization is permitted using forward planning techniques. Image guidance each day is encouraged.

Target Volume: The target volume consists of the entire brain and meninges, including the frontal lobe, cribriform plate that is typically below the orbital roof, the posterior halves of the globes of the eyes, with the optic disk and nerves, lower limit of the temporal fossa, extending superior to the vertex and posterior to the occiput. The caudal border will be below the skull base to at least the C2 vertebral level.

The target volume shall be defined by means of CT or conventional simulation. Care must be taken to avoid shielding the posterior orbit and cribriform plate. In case of conventional simulation, radio-opaque markers should be placed on the surface of the fleshy canthus to aid in localizing this point (see figure below).

Target Dose: The prescription point in each target volume is at or near the center of the target volume. For multi-convergent beams, the prescription point is usually at the intersection of the beam axes. The absorbed dose is specified in centigray (cGy)-to-muscle. Calculations shall take into account the effect of tissue heterogeneities

The daily dose to the prescription points for the cranial volume will be 1.8 Gy for patients with CNS3 leukemia at diagnosis. The total dose to the prescription point shall be 18 Gy in 10 treatments for patients with CNS3 leukemia at diagnosis.

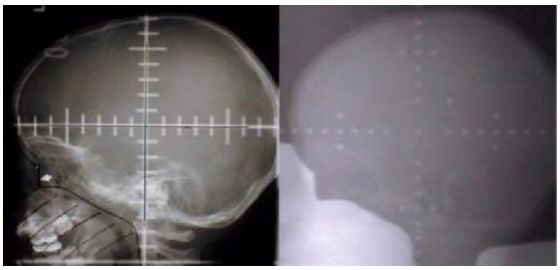
Fractionation: All radiation fields shall be treated once each day; the treatment shall be given 5 days a week.

Treatment Interruptions: No corrections will be made for treatment interruptions less than 7 days. For any interruptions greater than 7 days, contact the study director.

Dose Uniformity: The dose variations in each target volume shall be within +7%, -5% of the prescription-point dose.

Treatment Technique: The patient can be treated prone or supine. The cranial volume is treated with 2 lateral, equally weighted photon beams. Field in field techniques are permitted to improve dose uniformity. The fields shall extend at least 1 cm beyond the periphery of the scalp. Field-shaping will generally be done with multi-leaf collimators although cerroend blocks that are at least 5 HVL thick are also permitted (see figure below).

Figure: Example of radiation simulation radiograph with cerrobend block design (left) and megavoltage portal film (right) for cranial irradiation volume.



Eye protection: A simple method to minimize lens irradiation, while irradiating the posterior halves of the eyes, is to let the central axes of the horizontal cranial beams go through both orbits. The anterior edges of the beams are defined by an external block or by an independently controlled collimator and meet at a point 1 cm anterior to the frontal lobe meninges. Shielding blocks cover the anterior halves of the eyes and protect the nose and mouth. Essentially the same geometry can be achieved with the central axes through the center of the head by angling the lateral fields so that the rays through the eyes lie in the same horizontal plane. It is also acceptable to use a parallel-opposed beam-pair, without such angling, with shielding blocks that cover the anterior half of the proximal eye. The dose to the contralateral lens will be higher.

16.1 Post Treatment Review

Each National Group is responsile for quality assurance and data collection for cranial radiotherapy.

17 HEMATOPOIETIC TRANSPLANT GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. 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 where explicitly prohibited within the protocol).

17.1 Timing of Transplant

HR patients should proceed to HSCT after recovery from Consolidation Block #3. HSCT consultation should occur rapidly after determination that a patient is HR to make sure that a donor is ready in time for the intended timing.

Delays due to donor availabilty or other factors:
In the situation that additional time is needed after recovery from Consolidation Block #3 before starting HSCT preparative regimen, HR patients may receive therapy per HR Interim Maintenance Phase (Section 4.23). Daily imatinib should be continued until start of preparative regimen.

> Note: Treatment with Interim Maintenance phase therapy should be reserved for those patients in whom time between recovery from Consolidation Block 3 and start of preparative regimen is anticipated to be no longer than 4 weeks

Patients in whom HSCT is unlikely to occur within 4 weeks from the time of recovery after Consolidation Block 3:
Proceed with HR Delayed Intensification Phase #1 (Section 4.22). Proceed to HSCT during or immediately after recovery from this phase. HSCT preparative regimen must start within 21 days of attaining blood count recovery after Delayed Intensification #1. If HSCT has not occurred by that time, then HR Ph+ALL patients should continue therapy on the EsPhALL chemotherapy backbone with imatinib until 24 months from the start of Induction IA.

Patients with detectable MRD after Consolidation Block #3:
HR patients with MRD $\geq 10^{-2}$ after Consolidation Block #3 are off protocol therapy and should pursue further therapy per discretion of treating clinician. Such patients will be followed for relapse and survival status only. Patients with lower levels of detectable MRD after Consolidation Block #3 may proceed with HR Delayed Intensification Phase #1 (Section 4.22) and then to HSCT, or directly to HSCT, per the discretion of the treating clinician.

Patients who receive any other chemotherapy pre-HSCT other than those specified in the protocol will be considered off-protocol, and will be followed only for relapse and survival status.

17.2 Sanctuary Site Therapy

For patients with extramedullary involvement at diagnosis, it is recommended that cranial or testicular radiotherapy bososting be administered prior to HSCT in addition to the doses of Total Body Irradiation (TBI) associated with the preparative regimen. If administered, it is recommended that the cranial boost and/or testicular boosts be given over three days prior to the beginning of TBI. For patients with extramedullary involvement at diagnosis who receive a non-TBI containing regimen, receive 1800cGy radiation to the extramedullary site is recommended.
For patients entering FORUM study, the protocol study indications will be followed.

17.3 Exclusion Criteria for HSCT

It is recommended that the following criteria be considered to determine timing of HSCT.

Performance Level (See Appendix VIII) Patients with Karnofsky or Lansky scores < 60% are not eligible. Karnofsky scores must be used for patients >16 years of age and Lansky scores for patients ≤16 years of age.

Adequate Renal Function Defined As

- Creatinine clearance or radioisotope GFR 70 mL/min/1.73 m2 OR
- A serum creatinine based on age/gender as follows:

Estimated Creatinine Clearance (in mL/min/1.73 m^2) = 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.

Adequate liver function defined as:

- SGOT (AST) or SGPT (ALT) < 5 x upper limit of normal (ULN) for age.
- Direct bilirubin <2.5 mg/dL unless the increase in bilirubin is attributed to Gilbert's Syndrome

Adequate cardiac function defined as:

- Shortening fraction of 27% by echocardiogram, or
- Ejection fraction of 50% by radionuclide angiogram.

Adequate pulmonary function defined as:

- FEV_1, FVC, and DLCO corrected for Hgb ≥ 60% by pulmonary function tests (PFTs).
- For children who are unable to cooperate for PFTs, the criteria are: no evidence of pulmonary compromise.

17.4 Selection of Donors

Any donor selected as appropriate by the HSCT center is allowed.

Allowed donors include related HLA-identical and mismatched, unrelated HLA-matched and mismatched and related and unrelated umbilical cord bloods HLA matched and mismatched.

Both mobilized peripheral blood or marrow donors are allowed.

Ex vivo manipulated donor sources are allowed with either depletion or expansion of the donor source.

17.5 Selection of Preparative Regimen

Appropriate ALL-directed preparative regimens may be used at the discretion of the HSCT center.

Use of a non-myeloablative (non-MA) regimen is allowed if patients are not eligible for myeloablative (MA) therapy.

Use of non-TBI containing regimens such as those on the FORUM trials are allowed.

17.6 Tapering Immune Suppression After HSCT

It is recommended that immune suppression in the absence of GvHD should be discontinued by 100-180 days after BMT.

Immune suppression tapering can be longer depending upon the HSCT protocol the patients may be enrolled.

17.7 Grading of GvHD and Performance

Grading of performance should be as per Appendix X.

Grading of acute GvHD should be performed as per the Appendix X.

Grading of chronic GvHD should be performed as per the 2014 NIH consensus grading criteria (Appendix XI).

17.8 Recommended Monitoring of MRD

All HR patients who consent to MRD research samples should have marrow sent for MRD monitoring at Day +56 (or day that imatinib starts), Day +180 and Day +365.

Additional MRD monitoring may be performed per institutional standard of care.

Patients with two consecutive MRD measurements (after starting post-HSCT imatinib) obtained at least 2 weeks apart that are $\geq 10^{-2}$ will be removed from protocol therapy (Section 8.0) Note: *BCR-ABL1* fusion testing by PCR will not be used for MRD determination.

17.9 Recommended Measurement of Chimerism

Chimerism monitoring is recommended to be performed at 90±7 days, 6 months, and 12 months.

Chimerism monitoring is to be performed by the accepted institutions techniques.

17.10 Dosage of Imatinib

Imatinib is held when criteria to begin HSCT are met, and resumed on Day +56 post-HSCT.

17.11 Contraindicated Drugs

Some immunosuppressants potentially interact with imatinib. Careful monitoring is advised.

17.12 Off Protocol Patients

Any patient who comes off protocol therapy will be followed for relapse and survival status.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

For COG sites, only

APPENDIX II: CYP3A4 INDUCERS AND INHIBITORS

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently-updated medical references.

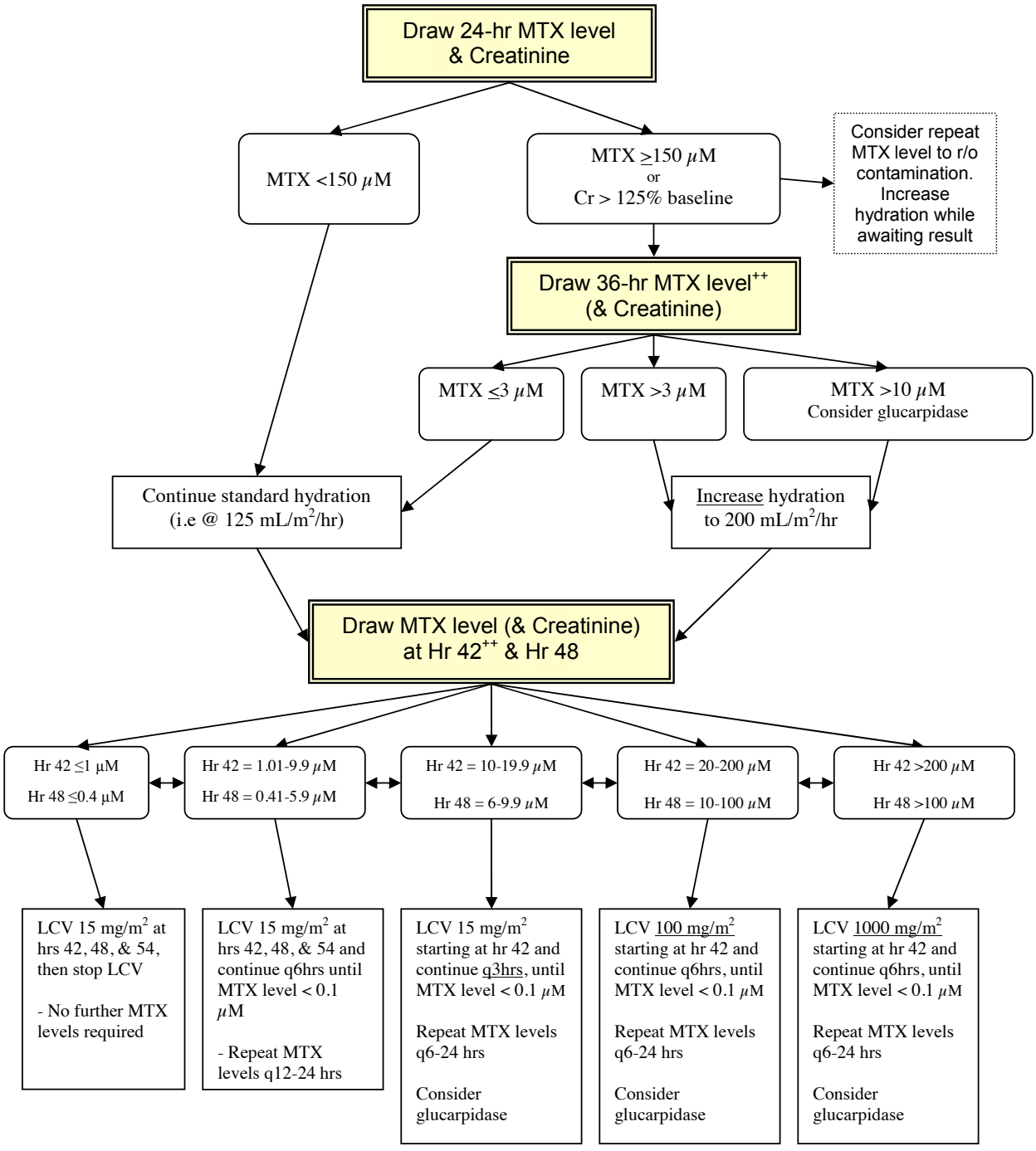
CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Weak Inhibitors	Inducers
alfentanil[4,5]	atazanavir	aprepitant	alprazolam	armodafinil
amiodarone[4]	boceprevir	atazanavir	amiodarone	barbiturates
aprepitant/fosaprepitant[5]	clarithromycin	cimetidine	amlodipine	bosentan
benzodiazepines	cobicistat	conivaptan	atorvastatin	carbamazepine
bortezomib	darunavir	crizotinib	bicalutamide	deferasirox
brentuximab	delavirdine	cyclosporine	cilostazol	echinacea
budesonide[5]	graperfruit[3]	diltiazem	cimetidine	efavirenz
buspirone[5]	grapefruit juice[3]	dronedarone	ciprofloxacin	etravirine
calcium channel blockers	indinavir	dronadorone	cyclosporine	fosphenytoin
cisapride	itraconazole	erythromycin	fluvoxamine	glucocorticoids[2]
citalopram/escitalopram	ketoconazole	fluconazole	isoniazid	modafinil
conivaptan[5]	lopinavir/ritonavir	fosamprenavir	nicardipine	nafcillin
glucocorticoids[2]	nefazodone	fosaprepitant	propofol	nevirapine
crizotinib	nelfinavir	grapefruit[3]	quinidine	oxcarbazepine
cyclosporine[4]	posaconazole	grapefruit juice[3]	ranolazine	phenobarbital
cyclophosphamide	ritonavir	imatinib		phenytoin
dapsone	saquinavir	mifepristone		pioglitazone
darifenacin[5]	telaprevir	nilotinib		primidone
darunavir[5]	telithromycin	norfloxacin		rifabutin
dasatinib[5]	voriconazole	verapamil		rifampin
dihydroergotamine				rifapentin
docetaxel				ritonavir
doxorubicin				St. John's wort
dronedarone[5]				topiramate
eletriptan[5]				
ergotamine[4]				
eplerenone[5]				
erlotinib				
esomeprazole				
estrogens				
etoposide				
everolimus[5]				
felodipine[5]				
fentanyl[4]				
fosaprepitant				
gefitinib				
haloperidol				
HIV antiretrovirals				
HMG Co-A inhibitors				
ifosfamide				
imatinib				

indinavir[5] irinotecan itraconazole ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] modafinil montelukast nefazodone nilotinib nisoldipine[5] omeprazole ondansetron paclitaxel pazopanib quetiapine[5] quinidine[4] saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sunitinib tacrolimus[4,5] telaprevir tetracycline tamoxifen temsirolimus teniposide tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 6.5 and Section 6.17 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates

APPENDIX III: HIGH DOSE METHOTREXATE FLOWCHART

(Please refer to Section 5.9 for complete details; all levels are timed from the start of the HDMTX infusion)



++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤1 and/or ≤ 0.4 μM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

MERCAPTOPURINE 25 mg/m^2

Note: The Mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.49	½ tab / d x 3	75 mg/wk
0.50 - 0.64	½ tab / d x 4	100 mg/wk
0.65 - 0.78	½ tab / d x 5	125 mg/wk
0.79 - 0.92	½ tab / d x 6	150 mg/wk
0.93 – 1.07	½ tab / d x 7	175 mg/wk
1.08 – 1.21	1 tab / d x 1; ½ tab / d x 6	200 mg/wk
1.22 – 1.35	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
1.36 – 1.49	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
1.50 – 1.64	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
1.65 – 1.78	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
1.79 – 1.92	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
1.93 – 2.07	1 tab / d x 7	350 mg/wk
2.08 – 2.21	1½ tab / d x 1; 1 tab / d x 6	375 mg/wk
2.22 - 2.35	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
2.36 – 2.49	1½ tab / d x 3; 1 tab / d x 4	425 mg/wk
2.50 – 2.64	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
2.65 – 2.78	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
2.79 – 2.92	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
2.93 – 3.00*	1½ tab / d x 7	525 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

MERCAPTOPURINE 50 mg/m^2

Note: The Mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.33 - 0.39	½ tab / d x 5	125 mg/wk
0.40 - 0.46	½ tab / d x 6	150 mg/wk
0.47 - 0.53	½ tab / d x 7	175 mg/wk
0.54 - 0.60	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.61 - 0.67	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.68- 0.74	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.75 - 0.82	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.83 - 0.89	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.90 - 0.96	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.97 - 1.03	1 tab / d x 7	350 mg/wk
1.04 – 1.10	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
1.11 - 1.17	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
1.18 - 1.24	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
1.25 - 1.32	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.33 - 1.39	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.40 - 1.46	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.47 - 1.53	1½ tab / d x 7	525 mg/wk
1.54 - 1.60	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.61 - 1.67	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.68 - 1.74	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.75 - 1.82	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.83 - 1.89	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.90 - 1.96	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.97 - 2.03	2 tab / d x 7	700 mg/wk
2.04 – 2.10	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
2.11 – 2.17	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
2.18 – 2.24	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
2.25 – 2.32	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
2.33 – 2.39	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
2.40 – 2.46	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
2.47 – 2.53	2½ tab / d x 7	875 mg/wk
2.54 – 2.60	2½ tab / d x 6; 3 tab / d x 1	900 mg/wk
2.61 – 2.67	2½ tab / d x 5; 3 tab / d x 2	925 mg/wk
2.68 – 2.74	2½ tab / d x 4; 3 tab / d x 3	950 mg/wk
2.75 – 2.82	3 tab / d x 4; 2½ tab / d x 3	975 mg/wk
2.83 – 2.89	3 tab / d x 5; 2½ tab / d x 2	1000 mg/wk
2.90 – 2.96	3 tab / d x 6; 2½ tab / d x 1	1025 mg/wk
2.97 – 3.00	3 tab / d x 7	1050 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

MERCAPTOPURINE 60 mg/m^2

Note: The Mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.

Body Surface Area (m^2)*	**Daily Dose (d) for 7 days** (1 tablet = 50 mg)	**Cumulative Weekly Dose**
0.33 - 0.38	½ tab / d x 6	150 mg/wk
0.39 - 0.44	½ tab / d x 7	175 mg/wk
0.45 - 0.50	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.51 - 0.56	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.57 - 0.62	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.63 - 0.68	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.69 - 0.74	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.75 - 0.80	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.81 - 0.86	1 tab / d x 7	350 mg/wk
0.87 - 0.92	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.93 - 0.98	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.99 - 1.04	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
1.05 - 1.10	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.11 - 1.16	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.17 - 1.22	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.23 - 1.27	1½ tab / d x 7	525 mg/wk
1.28 - 1.33	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.34 - 1.39	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.40 - 1.45	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.46 - 1.51	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.52 - 1.57	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.58 - 1.63	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.64 - 1.69	2 tab / d x 7	700 mg/wk
1.70 - 1.75	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.76 - 1.81	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk

1.82 - 1.87	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.88 - 1.93	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.94 - 1.99	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
2.00 - 2.05	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
2.06 - 2.11	2½ tab/ d x 7	875 mg/wk
2.12 - 2.17	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
2.18 - 2.23	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
2.24 - 2.29	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
2.30 - 2.35	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
2.36 - 2.41	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
2.42 - 2.47	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
2.48 - 2.52	3 tab/ d x 7	1050 mg/wk
2.53 - 2.58	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.59 - 2.64	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.65 - 2.70	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.71 - 2.76	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.77 - 2.82	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.83 - 2.88	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.89 - 2.94	3½ tab/ d x 7	1225 mg/wk
2.95 - 3.00	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

MERCAPTOPURINE 75 mg/m^2

Note: The Mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk
2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.17 – 2.21	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.22 – 2.26	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.27 – 2.30	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.31 – 2.35	3½ tab/ d x 7	1225 mg/wk
2.36 – 2.40	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk
2.41 – 2.45	3½ tab/ d x 5; 4 tab / d x 2	1275 mg/wk
2.46 – 2.49	3½ tab/ d x 4; 4 tab / d x 3	1300 mg/wk
2.50 – 2.54	4 tab/ d x 4; 3½ tab / d x 3	1325 mg/wk
2.55 – 2.59	4 tab/ d x 5; 3½ tab / d x 2	1350 mg/wk
2.60 – 2.64	4 tab/ d x 6; 3½ tab / d x 1	1375 mg/wk
2.65 – 2.69	4 tab/ d x 7	1400 mg/wk

2.70 – 2.73	4 tab/ d x 6; 4½ tab / d x 1	1425 mg/wk
2.74 – 2.78	4 tab/ d x 5; 4½ tab / d x 2	1450 mg/wk
2.79 – 2.83	4 tab/ d x 4; 4½ tab / d x 3	1475 mg/wk
2.84 – 2.88	4½ tab/ d x 4; 4 tab / d x 3	1500 mg/wk
2.89 – 2.92	4½ tab/ d x 5; 4 tab / d x 2	1525 mg/wk
2.93 – 2.97	4½ tab/ d x 6; 4 tab / d x 1	1550 mg/wk
2.98 – 3.00	4½ tab/ d x 7	1575 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

THIOGUANINE 60 mg/m^2

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 40 mg)	Cumulative Weekly Dose
0.31 - 0.35	½ tab / d x 7	140 mg/wk
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.60 - 0.64	1 tab/ d x 6; ½ tab / d x 1	260 mg/wk
0.65 - 0.69	1 tab / day	280 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
0.79 - 0.83	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
0.98 - 1.02	1½ tab /day	420 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.31 - 1.35	2 tab / day	560 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
1.46 - 1.49	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
1.50 - 1.54	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
1.55 - 1.59	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
1.60 - 1.64	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
1.65 - 1.69	2½ tab / d	700 mg/wk
1.70 - 1.73	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
1.74 - 1.78	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
1.79 - 1.83	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
1.84 - 1.88	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
1.89 - 1.92	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
1.93 - 1.97	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk
1.98 - 2.02	3 tab / d x 7	840 mg/wk
2.03 - 2.07	3 tab / d x 6; 3½ tab / d x 1	860 mg/wk
2.08 - 2.11	3 tab / d x 5; 3½ tab / d x 2	880 mg/wk
2.12 - 2.16	3 tab / d x 4; 3½ tab / d x 3	900 mg/wk
2.17 - 2.21	3½ tab / d x 4; 3 tab / d x 3	920 mg/wk
2.22 - 2.26	3½ tab / d x 5; 3 tab / d x 2	940 mg/wk
2.27 – 2.30	3½ tab / d x 6; 3 tab / d x 1	960 mg/wk
2.31 – 2.35	3½ tab / d x 7	980 mg/wk
2.36 – 2.40	3½ tab / d x 6; 4 tab / d x 1	1000 mg/wk

2.41 – 2.45	3½ tab / d x 5; 4 tab / d x 2	1020 mg/wk
2.46 – 2.49	3½ tab / d x 4; 4 tab / d x 3	1040 mg/wk
2.50 – 2.54	4 tab / d x 4; 3½ tab / d x 3	1060 mg/wk
2.55 – 2.59	4 tab / d x 5; 3½ tab / d x 2	1080 mg/wk
2.60 – 2.64	4 tab / d x 6; 3½ tab / d x 1	1100 mg/wk
2.65 – 2.69	4 tab / d x 7	1120 mg/wk
2.70 – 2.73	4 tab / d x 6; 4½ tab / d x 1	1140 mg/wk
2.74 – 2.78	4 tab / d x 5; 4½ tab / d x 2	1160 mg/wk
2.79 – 2.83	4 tab / d x 4; 4½ tab / d x 3	1180 mg/wk
2.84 – 2.88	4½ tab / d x 4; 4 tab / d x 3	1200 mg/wk
2.89 – 2.92	4½ tab / d x 5; 4 tab / d x 2	1220 mg/wk
2.93 – 2.97	4½ tab / d x 6; 4 tab / d x 1	1240 mg/wk
2.98 – 3.00	4½ tab / d x 7	1260 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their TG doses calculated on actual BSA with no maximum dose.*

APPENDIX VI: IMATINIB TABLETS DOSING GUIDELINES

IMATINIB 340 mg/m^2/day up to a maximum of 800 mg/day

Body Surface Area (m2)	Total daily dose (rounded to the nearest 50 mg)	Recommended administration
≤ 0.36	100 mg	1 x 100mg tablet once daily
0.37 - 0.51	150 mg	1½ x 100mg tablets once daily
0.52 – 0.66	200 mg	2 x 100mg tablets once daily
0.67 – 0.81	250 mg	2½ x 100mg tablets once daily
0.82 – 0.95	300 mg	3 x 100mg tablets once daily
0.96 – 1.10	350 mg	3½ x 100mg tablets once daily
1.11 – 1.25	400 mg	1 x 400mg tablet once daily
1.26 – 1.39	450 mg	1 x 400mg tablet and ½ x 100mg tablet once daily
1.40 – 1.54	500 mg	1 x 400mg tablet and 1 x 100mg tablet once daily
1.55 – 1.69	550 mg	1 x 400mg tablet and 1½ x 100mg tablet once daily
1.70 – 1.83	600 mg	1½ x 400 mg tablets once daily
1.84 – 1.98	650 mg	1 x 400mg tablet in the morning and 2½ x 100mg tablet at night
1.99 – 2.13	700 mg	1 x 400mg tablet in the morning and 3 x 100mg tablets at night
2.14 – 2.27	750 mg	1 x 400mg tablet in the morning and 3½ x 100mg tablets at night
≥ 2.28	800 mg	1 x 400mg tablet in the morning and 1 x 400mg tablet at night

APPENDIX VII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY
(for children from 7 through 12 years of age)

A trial to compare two different combination chemotherapy treatment plans for patients with Philadelphia chromosome positive (Ph+) Acute Lymphoblastic Leukemia (ALL)

1. We have been talking with you about your Ph+ ALL. Ph+ ALL is a type of cancer that grows in the bone marrow. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have Ph+ ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat Ph+ ALL and reduce the bad effects of the anticancer drugs. We will do this by trying different combinations of anticancer drugs to see which one works better and causes fewer bad effects. We don't know which way is better. That is why we are doing this study.

3. Children who are part of this study will receive a treatment called combination chemotherapy. Combination chemotherapy is where different cancer fighting medicines are given together to kill cancer. Some children who are part of this study will get the usual combination chemotherapy that doctors use for Ph+ ALL. Some children will get less or a different combination of chemotherapy drugs. Also, some children will get a stem cell transplant. Sometimes X-ray treatments are also given to help kill cancer that is in the brain or to keep the cancer from moving into the brain. The chemotherapy you get will be decided by chance, like flipping a coin for "heads" or "tails". You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. These tests help doctors in deciding the most appropriate treatment for your Ph+ ALL. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible, and with fewer bad effects, but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. There is a risk that you will have more bad effects from the medicines if you are treated with any of the additional treatments along with the usual medicines. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.
7. We are asking your permission to collect additional bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard bone marrow tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY
(for teens from 13 through 17 years of age)

A trial to compare two different combination chemotherapy treatment plans for patients with Philadelphia chromosome positive (Ph+) Acute Lymphoblastic Leukemia

1. We have been talking with you about your Ph+ ALL. Ph+ ALL is a type of cancer that grows in the bone marrow. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have Ph+ ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat Ph+ ALL and reduce the bad effects of the anticancer drugs. We will do this by trying different combinations of anticancer drugs to see which one works better and causes fewer side effects. We don't know which way is better. That is why we are doing this study.

3. Children and teens who are part of this study will receive a treatment called combination chemotherapy. Combination chemotherapy is where different cancer fighting medicines are given together to kill cancer. Some children and teens who are part of this study will get the usual combination chemotherapy that doctors use for Ph+ ALL. Some children and teens will get less or a different combination of chemotherapy drugs. Also, some children and teens will get a stem cell transplant. Sometimes X-ray treatments are also given to help kill cancer that is in the brain or to keep the cancer from moving into the brain. The chemotherapy you get will be decided by chance, like flipping a coin for "heads" or "tails". You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. These tests help doctors in deciding the most appropriate treatment for your Ph+ ALL. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible, and with fewer bad effects, but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." There is a risk that you will have more bad effects from the medicines if you are treated with any of the additional treatments along with the usual medicines. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard bone marrow tests are being performed, so there would be no extra procedures. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research.

APPENDIX VIII: DRUG INTERACTION TABLES

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

Some drugs, food, and supplements may interact with cyclophosphamide. Examples include:

Drugs that may interact with cyclophosphamide
• Allopurinol • Chloramphenicol • Cyclosporine • Digoxin • Etanercept • Hydrochlorothiazide • Indomethacin • Nevirapine • Pentostatin • Warfarin

Food and supplements that may interact with cyclophosphamide
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Some drugs, food, and supplements may interact with <u>DAUNOrubicin</u>. Examples include:

Drugs that may interact with daunorubicin*
• Some antibiotics and antifungals (clarithromycin, erythromycin, itraconazole, ketoconazole) • Some antiepileptics (carbamazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (darunavir, lopinavir; nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir) • Some heart medications (amiodarone, carvedilol, digoxin, dronedarone, nicardipine, propranolol, verapamil) • Other agents, such as atorvastatin, clozapine, cyclosporine, dexamethasone, ivacaftor, leflunomide, natalizumab, nefazodone, progesterone, rifampin, tacrolimus, tofacitinib, and trazodone

Food and supplements that may interact with daunorubicin**
• Echinacea • Grapefruit, grapefruit juice, Seville oranges, star fruit

- St. John's Wort
- Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Some drugs, food, and supplements may interact with <u>dexamethasone</u>. Examples include:

Drugs that may interact with dexamethasone*
• Antibiotics o Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine • Antifungals o Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine, sirolimus, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, amlodipine, dronedenarone, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Some oral contraceptives or birth control medications • Many other drugs, including the following: o Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Some drugs, food, and supplements may interact with <u>dexrazoxane</u>. Examples include:

Drugs that may interact with dexrazoxane*
• Clozapine • Dimethyl sulfoxide (DMSO)

Food and supplements that may interact with dexrazoxane**
• Unknown

Some drugs, food, and supplements may interact with <u>DOXOrubicin</u>. Examples include:

Drugs that may interact with doxorubicin*
• Some antiepileptics (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (stavudine, zidovudine) • Other agents, such as clozapine, cyclosporine, verapamil, and warfarin

Food and supplements that may interact with doxorubicin**
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Some drugs, food, and supplements may interact with <u>etoposide</u>. Examples include:

Drugs that may interact with etoposide*

• Antibiotics
  o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  o Aripiprazole, clozapine, nefazodone
• Antifungals
  o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  o Leflunomide, tofacitinib
• Anti-rejection medications
  o Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
  o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  o Amiodarone, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  o Aprepitant, atovaquone, bosentan, deferasirox, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, sitaxentan

Food and supplements that may interact with etoposide**
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Some drugs, food, and supplements may interact with ifosfamide. Examples include:

Drugs that may interact with ifosfamide*
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, paliperidone, quetiapine, thioridizine, ziprasidone • Antifungals o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, dronedenarone, verapamil • Stomach and reflux medications o Esomeprazole, omeprazole • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: o Bosentan, sitaxentan, aprepitant, dexamethasone, lomitapide, mifepristone, natalizumab, pimozide

Food and supplements that may interact with ifosfamide**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Some drugs, food, and supplements may interact with imatinib mesylate. Examples include:

Drugs that may interact with imatinib*

• Antibiotics
  o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, rifapentin, telithromycin
• Antidepressants and antipsychotics
  o Aripiprazole, nefazodone
• Antifungals
  o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  o Leflunomide, tofacitinib
• Anti-rejection medications
  o Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir
• Anti-seizure medications
  o Carbamazepine, oxcarbazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Pain medications
  o Hydrocodone, oxycodone
• Heart medications
  o Amiodarone, diltiazem, dronedarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  o Acetaminophen, aprepitant, bosentan, conivaptan, deferasirox, dexamethasone, ivacaftor, lansoprazole, lomitapide, mifepristone, modafinil, natalizumab, netupitant, sildenafil, warfarin

Food and supplements that may interact with imatinib**
• St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Some drugs, food, and supplements may interact with <u>leucovorin</u>. Examples include:

Drugs that may interact with leucovorin*
• Some antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone)

Food and supplements that may interact with leucovorin**
• Folic acid

Some drugs, food, and supplements may interact with mercaptopurine. Examples include:

Drugs that may interact with mercaptopurine*
• Artiritis medications: leflunomide, tofacitinib • Other medications, such as allopurinol, azathioprine, clozapine, febuxostat, natalizumab, olsalazine, sulfasalazine, warfarin

Food and supplements that may interact with mercaptopurine**
• Echinacea

Some drugs, food, and supplements may interact with <u>methotrexate (by mouth or by vein)</u>.Examples include:

Drugs that may interact with methotrexate*
• Some antibiotics (amoxicillin, Bactrim, chloramphenicol, ciprofloxacin, penicillin, piperacillin, tetracycline) • Some anti-inflammatory drugs (aspirin, acetaminophen, ibuprofen, naproxen, ketorolac) • Some heartburn medications (esomeprazole, lansoprazole, omeprazole, pantoprazole) • Several other specific agents, including the following: amiodarone, clozapine, cyclosporine, eltrombopag, leflunomide, phenytoin, pimecrolimus, probenecid, pyrimethamine, retinoids, theophylline, warfarin

Food and supplements that may interact with methotrexate**
• Alcohol • Echinacea • Some vitamins, including those that contain folic acid or high doses of vitamin C

Some drugs, food, and supplements may interact with <u>pegaspargase</u>. Examples include:

Drugs that may interact with pegaspargase*
• Leflunomide, natalizumab, tofacitinib

Food and supplements that may interact with pegaspargase**
• Echinacea

Some drugs, food, and supplements may interact with <u>predniSO(LO)NE</u>. Examples include:

Drugs that may interact with prednisone*
• Arthritis medications   o Leflunomide, tofacitinib

- Antiretrovirals and antivirals
  - Boceprevir, ritonavir, telaprevir
- Anti-seizure medications
  - Phenobarbital, phenytoin, primidone
- Growth hormones
- Heart medications
  - Diltiazem, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Some oral contraceptives or birth control medications
- Many other drugs, including the following:
  - Aprepitant, aripiprazole, aspirin, cyclosporine, deferasirox, ibuprofen, itraconazole, mifepristone, natalizumab, rifampin, warfarin

Food and supplements that may interact with prednisone**
• Echinacea

Some drugs, food, and supplements may interact with thioguanine. Examples include:

Drugs that may interact with thioguanine*
• Arthritis medications: leflunomide, tofacitinib • Other medications, such as allopurinol, clozapine, natalizumab, olsalazine, sulfasalazine

Food and supplements that may interact with thioguanine**
• Echinacea

Some drugs, food, and supplements may interact with vinCRIStine. Examples include:

Drugs that may interact with vincristine*

• Antibiotics
  o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  o Aripiprazole, nefazodone, trazodone
• Antifungals
  o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  o Leflunomide, tocilizumab, tofacitinib
• Anti-rejection medications
  o Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir
• Anti-seizure medications

○ Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications ○ Amiodarone, digoxin, dronedenarone, propranolol, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: ○ Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin

Food and supplements that may interact with vincristine**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

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.

*The conversion of the Karnofsky and Lansky to ECOG scales is intended for NCI reporting purposes only.

Appendix X: COG Stem Cell Committee Consensus Guidelines for Establishing Organ Stage and Overall Grade of Acute Graft versus Host Disease (GVHD)

Reporting Requirements for Acute GVHD in COG Studies

In an attempt to standardize reporting of acute GVHD, the COG Stem Cell Transplantation Committee has adopted a modification of guidelines that were originally developed at the University of Michigan.

Table 1 outlines standard criteria for GVHD organ staging. However, confounding clinical syndromes (such as non-GVHD causes of hyperbilirubinemia) may make staging GVHD in a given organ difficult. In addition, timing of organ specific symptoms affects whether that symptom is more or less likely to be true GVHD. Please refer to ***Tables 2 and 3*** to assist you in deciding whether to attribute these clinical findings to GVHD, especially in situations where a biopsy is not possible. For additional help, please see the text which follows the tables. ***Table 4*** reviews the approach to assessing GVHD as acute, chronic, or the overlap between the two.

Finally, *engraftment syndrome* will be reported separately from the GVHD scoring presented below.

Engraftment Syndrome

A clinical syndrome of fever, rash, respiratory distress, and diarrhea has been described, just prior to engraftment in patients undergoing unrelated cord blood and mismatched transplantation. If, in the judgment of the local investigator, a patient experiences this syndrome, details of the event should be reported when requested in the study CRFs.

Modified Glucksberg Staging Criteria for Acute Graft versus Host Disease

Table 1 Organ Staging (See tables and text below for details)

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No GVHD rash	< 2 mg/dL	Adult: < 500 mL/day Child: < 10 mL/kg/day
1	Maculopapular rash < 25% BSA	2-3 mg/dL	Adult: 500–999 mL/day Child: 10 -19.9 mL/kg/day ***Or persistent nausea, vomiting, or anorexia, with a positive upper GI biopsy.***
2	Maculopapular rash 25 – 50% BSA	3.1-6 mg/dL	Adult: 1000-1500 mL/day Child: 20 – 30 mL/kg/day
3	Maculopapular rash > 50% BSA	6.1-15 mg/dL	Adult: > 1500 mL/day Child: > 30 mL/kg/day
4	Generalized erythroderma plus bullous formation and desquamation > 5% BSA	>15 mg/dL	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

For GI staging: The "adult" stool output values should be used for patients > 50 kg in weight. Use 3 day averages for GI staging based on stool output. If stool and urine are mixed, stool output is presumed to be 50% of total stool/urine mix (see Section 3.2).

For stage 4 GI: the term "severe abdominal pain" will be defined as:
(a) Pain control requiring institution of opioid use, or an increase in on-going opioid use, PLUS
(b) Pain that significantly impacts performance status, as determined by the treating MD.

If colon or rectal biopsy is +, but stool output is < 500 mL/day (< 10 mL/kg/day), then consider as GI stage 0.

There is no modification of liver staging for other causes of hyperbilirubinemia

Overall Clinical Grade (based on the highest stage obtained):
Grade 0: No stage 1-4 of any organ
Grade I: Stage 1-2 skin and no liver or gut involvement
Grade II: Stage 3 skin, or Stage 1 liver involvement, or Stage 1 GI
Grade III: Stage 0-3 skin, with Stage 2-3 liver, or Stage 2-3 GI
Grade IV: Stage 4 skin, liver or GI involvement

Table 2 Evaluating Liver GVHD in the Absence of Biopsy Confirmation (See Table 3.0 below)

Establishing liver GVHD with no skin or GI GVHD

No Skin/GI GVHD Day 0-35	**Assume no liver GVHD,** unless proven by biopsy	
No Skin/GI GVHD Day 36-100	If NO other etiology identified, NO improvement with stopping hepatotoxic medications/TPN: **Stage as liver GVHD**	If other etiology identified or improves with stopping hepatotoxic drugs/TPN: **Do not stage as liver GVHD**

Establishing liver GVHD with skin or GI GVHD and other cause of hyperbilirubinemia

Skin and/or GI GVHD present	Worsening bilirubin level (includes worsening just prior to onset of skin or GI tract GVHD) OR stable elevated bilirubin despite resolution of non-GVHD cause of increased bilirubin: **Stage as liver GVHD**	Stable or improving bilirubin after diagnosis of skin or GI GVHD, irrespective of treatment: **Do not stage as liver GVHD**

Changing liver GVHD stage with other cause of hyperbilirubinemia

Skin and GI GVHD stable, improving, or absent	Liver GVHD staging is carried forward without increase in stage until other disease process resolves (e.g., if TTP is diagnosed in the presence of stage 2 liver GVHD, the liver GVHD stage 2 is carried forward despite rising bilirubin level until TTP is resolved. If there is no liver GVHD – stage 0 – and new onset TTP, the stage 0 is carried forward until TTP is resolved).

Skin and/or GI GVHD worsening	**Liver GVHD is staged according to the Glucksberg criteria. The elevated bili is attributed to GVHD alone.** Thus, when skin or GI GVHD is worsening, there is no downgrading of liver GVHD staging for other causes of hyperbilirubinemia. (e.g., if TTP is diagnosed in the presence of stage 2 liver GVHD and worsening skin or GI GVHD, the liver is staged according to the actual bilirubin level even if some of the rise in bilirubin is attributed to TTP). Similarly, even if there is no liver GVHD at onset of a new process, (such as TPN cholestasis), but skin or GI GVHD worsen during that process, then liver GVHD is diagnosed and staged according to the height of the bilirubin. **There is one exception to this**: the diagnosis of TTP, with high LDH and **unconjugated** bilirubin precludes the diagnosis and staging of new liver GVHD in the absence of a confirmatory liver biopsy.

Table 3 Evaluating GI GVHD in the Absence of Biopsy Confirmation (See Table 4.0 below)

Establishing GI GVHD with new onset diarrhea and no skin or liver GVHD

No Skin/liver GVHD Day 0 through engraftment	Assume no GI GVHD, unless proven by biopsy	
No Skin/liver GVHD Engraftment through day 100	NO other etiology of diarrhea identified: **Stage as GI GVHD**	Any other etiology of diarrhea identified: **Do not stage as GI GVHD**

Establishing GI GVHD with pre-existing diarrhea and skin or liver GVHD

Skin and/or liver GVHD present	Worsening diarrhea (includes worsening just prior to onset of skin or liver GVHD) OR persistent diarrhea despite resolution of non-GVHD cause: **Stage as GI GVHD**	Improving diarrhea after the diagnosis of skin or liver GVHD (irrespective of treatment) OR persistent diarrhea without resolution of underlying non-GVHD cause: **Do not stage as GI GVHD**

Differentiating Acute GVHD, Chronic GVHD, and Overlap Syndrome

There is often confusion differentiating acute from chronic GVHD, especially in the setting of reduced intensity transplants, DLI and new prophylactic treatments. The NIH Working Group recently published new classifications for GVHD:

Table 4 Acute GVHD, Chronic GVHD, and Overlap Syndrome

Category	Time of Symptoms after HCT or DLI	Presence of Acute GVHD features	Presence of Chronic GVHD features
Acute GVHD			
Classic acute GVHD	≤100 d	Yes	No
Persistent, recurrent, or late-onset acute GVHD	>100 d	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

- Scoring of acute GVHD may need to occur past day 100. In particular, patients should continue to be scored for acute GVHD when classic acute GVHD symptoms (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea - particularly if bloody and ileus) persist past day 100 or if identical symptoms previously scored as acute GVHD resolve and then recur within 30 days during immunosuppression taper but past day 100.

- Those patients being scored as having acute GVHD should NOT have diagnostic or distinctive signs of chronic GVHD.

- **Patients with both acute and chronic symptoms should be diagnosed as having Overlap Syndrome and scored according to their chronic GVHD score**.

Further Explanation of Criteria presented in Tables 2 and 3

1.0 Assessment of Skin GVHD

1.1 Presence or Absence of Skin GVHD:

Skin GVHD will be considered present if a rash characteristic of acute GVHD develops after allogeneic marrow transplantation involving more than 25% of the body surface not clearly attributable to causes such as drug administration or infection. The extent of the body surface area involved can be estimated by the "Rule of Nines". In estimating the extent of skin GVHD, the area involved is calculated for individual anatomic areas, such as the arm or leg, and then the total is derived from a simple summation. Areas that are non-blanching should not be considered involved regardless of the overlying color of the rash (red, brown, etc). Limited distribution erythema (with the exception of palms and soles) in the absence of associated rash elsewhere on the body will not be considered GVHD.

2.0 Assessment of Liver GVHD

2.1 Assessing for the Presence or Absence of Liver GVHD

A. Hyperbilirubinemia (total bilirubin ≥ 2.0 mg/dL) in the **absence** of other signs of acute GVHD in the skin or GI tract:

i) Day 0-35: If hyperbilirubinemia alone is present with no other signs of acute GVHD in other

organ systems, acute GVHD will not be diagnosed based solely on laboratory abnormalities. Acute GVHD will be diagnosed if findings on histopathology studies of liver from a biopsy or autopsy are confirmatory.

ii) Day 35-100: If hyperbilirubinemia (must be conjugated bilirubin) is not improving or is exacerbated (especially if serum alkaline phosphatase is increased), in the absence of acute GVHD in other organ systems, no other etiologies are identified, and does not improve with discontinuation of hepatotoxic drugs, acute GVHD will be diagnosed. However, it is distinctly unusual to develop ascites or a coagulopathy in the early stages of acute GVHD of the liver alone. In the absence of histopathology studies of liver from a biopsy or autopsy specimen, ascites or a coagulopathy secondary to liver dysfunction will be considered to indicate the presence of another disease process (e.g. veno-occlusive disease). Recommended non-invasive studies to define an etiology for hyperbilirubinemia are:

a. Imaging of liver (CT or ultrasound)
b. Hepatitis screen (only if ALT is elevated)
c. PT
d. Blood cultures
e. Review of medication list for potentially hepatotoxic drugs
f. Review of risk factors for viral liver infection (HSV, CMV, VZV, adenovirus, EBV, HBV, and HCV)
g. Hemolysis screen

B. Pre-existing hyperbilirubinemia clearly attributed to an etiology other than acute GVHD in the presence of signs of acute GVHD in other organ systems.

i) If pre-existing non-GVHD liver disease (documented clinically, by lab assessment, or by imaging studies) is stable or improving at the onset of signs of acute GVHD in other organs, then acute GVHD of the liver will not be considered to be present unless proven by liver biopsy or autopsy.

ii) If hyperbilirubinemia worsens several days before or at the time of onset of signs of acute GVHD in other organ systems, GVHD will be considered to be present unless histopathology studies of liver are available and negative on a biopsy during that time interval or autopsy results exclude GVHD.

iii) If hyperbilirubinemia persists and is not improving after resolution of a pre-existing non-GVHD liver disease process (e.g. localized infection of liver, systemic sepsis, biliary tract obstruction) when signs of acute GVHD are present in other organ systems or no other intervening cause has been diagnosed, then acute GVHD will be considered to be present in the absence of a new, clearly identifiable cause of non-GVHD liver disease or unless a liver biopsy or autopsy specimen is negative.

C. Prior acute GVHD in liver with new onset of a disease process that exacerbates pre-existing or recently resolved hyperbilirubinemia:

i) If an etiology other than acute GVHD is clearly identified as causing or exacerbating hyperbilirubinemia and acute liver GVHD has been diagnosed and has been stable, improving, or resolved, then the liver will not be restaged for acute GVHD until the resolution or stabilizing of the concurrent disease process (i.e., the liver stage prior to the onset of the new disease process will be carried forward until the new disease process resolves). Example: Acute GVHD of the

liver and gut is diagnosed on day 20. Treatment of acute GVHD results in falling bilirubin levels to liver stage 1. Sepsis or TTP develops with transient worsening of the hyperbilirubinemia. The liver stage is not increased, despite a higher bilirubin level, because the cause of worsening hyperbilirubinemia is attributed to sepsis or TTP.

ii) If an etiology other than acute GVHD is clearly identified as causing or exacerbating hyperbilirubinemia in the presence of already worsening acute liver GVHD **or** GVHD of the skin or GI tract is simultaneously worsening, then the liver GVHD will be staged according to the actual bilirubin level, even though another cause of hyperbilirubinemia is present.

3.0 Assessment of GVHD of the Gastrointestinal Tract

3.1 Assessing for the Presence or Absence of GVHD of the Gastrointestinal Tract

A. Diarrhea (≥ 500 mL/day in adults or > 10 mL/kg in pediatric patients) in the absence of other signs of acute GVHD in other organ systems

i) Day 0-engraftment: If diarrhea alone is present without other signs of acute GVHD in other organ systems, acute GVHD will not be considered present. Diarrhea will be attributed to acute GVHD if histopathology studies of gastrointestinal tract from a biopsy or autopsy are diagnostic.

ii) Engraftment-day 100: If diarrhea persists and is not improving, is exacerbated, or develops de novo in the absence of acute GVHD in other organ systems, histopathology studies of gut biopsies or from autopsy specimens are not available, and no other etiologies are clearly identified, acute GVHD will be considered to be the cause. A stool specimen should be examined to rule out infectious causes (e.g. rotavirus, adenovirus, and C. difficile toxin). It is recommended, if at all possible, that biopsies be obtained for diagnostic purposes.

B. Pre-existing diarrhea clearly attributed to an etiology other than acute GVHD in the presence of signs of acute GVHD in other organ systems:

i) If pre-existing diarrhea caused by a process other than GVHD has been documented clinically or by lab assessment and is stable or improving at the onset of signs of acute GVHD in the skin or liver, then acute GVHD of the intestine will not be considered to be present in the absence of biopsy confirmation or autopsy report.

ii) If diarrhea or gastrointestinal symptoms are already present, but worsen significantly at the time of onset of signs of acute GVHD in the skin or liver, GVHD will be considered present, unless biopsy or autopsy are negative.

iii) If diarrhea persists after resolution of a pre-existing disease process with signs of acute GVHD present in other organ systems, GVHD will be considered present, unless biopsy or autopsy are negative.

C. Prior or present acute GVHD in other organ systems with new onset of diarrhea:

If diarrhea is **clearly** attributable to an etiology other than acute GVHD (e.g., infection) and a history of acute GVHD exists or acute GVHD is present in other organ systems and is stable, then the gastrointestinal tract will not be evaluable for acute GVHD until the resolution or stabilizing

of the other disease process (e.g., infection) in the absence of biopsy or autopsy confirmation.

D. Persistent anorexia, nausea or vomiting in the absence of signs of acute GVHD in other organ systems:

Persistent anorexia, nausea or vomiting in the absence of other known causes of these symptoms will be considered stage 1 acute GVHD if confirmed by endoscopic biopsy.

If a biopsy is not possible (e.g. secondary to thrombocytopenia) but the clinical findings are compatible with acute GVHD, then the patient will be treated and recorded as having acute GVHD.

3.2 Staging of the Gastrointestinal Tract for the Severity of Acute GVHD

The severity of gastrointestinal tract GVHD will be staged according to modified Glucksberg criteria. To minimize errors caused by large day-to-day variation, diarrhea volume is measured as an average over 3 days and reported as the volume in milliliters per day. When urinary mixing is noted the stool volume will be considered half of the total volume unless nursing staff is able to give a better estimate from direct observation. Abdominal cramps are considered significant for staging if the severity results in a clinical intervention (e.g. analgesia, fasting, etc.). Blood in the stools is considered significant if the blood is visible or hematochezia/ melena is present and not clearly attributed to a cause other than GVHD (e.g. epistaxis/ hemorrhoids).

APPENDIX XI: ASSESSMENT AND GRADING OF CHRONIC GvHD AS PER THE NIH CONSENSUS CRITERIA

Assessment of the presence or absence of chronic GVHD should follow the 2014 NIH consensus criteria guidelines.[81]

An organ system approach to the diagnosis of cGVHD should be taken, with specific documentation of cGVHD manifestations in the skin, nails, scalp, mouth, eyes, genitalia, gastrointestinal tract, liver, lung, and muscles / fascia / joints be undertaken with each assessment (see **Table 1** below). Individual manifestations in each organ system are divided into manifestations that are **diagnostic** (when present are adequate to establish the diagnosis of cGVHD), **distinctive** (when present strongly suggest the diagnosis of cGVHD but are not enough to establish the diagnosis without additional testing), **common** (are frequently present in both acute and chronic GVHD, but not sufficient to differentiate the two entities), and **other** (rare, controversial, or nonspecific features of cGVHD).

To diagnose chronic GVHD the individual must either have (1) one **diagnostic** sign, or (2) one **distinctive** sign with supporting evidence in the form of either a biopsy that supports chronic GVHD, a laboratory or other test (e.g. PFTs, Schirmer's test), evaluation by a specialist (e.g. opthamologist, gynecologist), or radiographic image showing cGHVD in the same or other organ. It is noteworthy that diagnostic signs of chronic GVHD are specific and present only in a few organ systems. These include the **skin** (*poikiloderma – atrophy, pigmentary changes, and telangiectasia; lichen-planus features; deep sclerotic features; morphea-like features; and lichen-sclerosis features),* ***mouth*** *(lichen-planus features),* ***genitalia*** (*lichen-planus and lichen-sclerosis features; vaginal scarring; phimosis; urethral meatus scarring or stenosis)*, **gastrointestinal tract** *(esophageal web, esophageal stenosis)*, **lungs** (*bronchiolitis obliterans diagnosed by lung biopsy*), and **muscles/fascia/joints** (*fasciitis, joint stiffness and contractures)*. Diagnostic signs may also not be present in the early stages of chronic GVHD development, leading to difficulty in establishing a chronic GVHD diagnosis with certainty at the time of onset.

Some key elements to chronic GVHD diagnosis and the timing of drawing the chronic GVHD blood sample are presented here:

- The presence of acute GVHD features alone (without any additional chronic GVHD manifestations) after day 100 (e.g. maculopapular rash, nausea, vomiting, diarrhea, ileus, hyperbilirubinemia and cholestatic liver disease), including when these features emerge with reduction in immunosuppression, should be classified as late-onset, recurrent, or persistent acute GVHD, not as chronic GVHD. A cGVHD diagnostic blood sample is not required and these patients should continue to have blood samples drawn at 6-months and 12-months post-transplant so long as chronic GVHD does not develop in the interim.

- The presence of acute GVHD features along with diagnostic or distinctive chronic GVHD features, regardless of the time post-transplant, should be classified as overlap syndrome (both acute and chronic GVHD present at the same time). These cases will be considered as chronic GVHD cases. A diagnostic cGVHD blood samples should be drawn at the onset of cGVHD diagnosis.

- There are no diagnostic or distinctive chronic GVHD manifestations in the liver. Biochemical liver abnormalities alone (elevated transaminases, cholestatic enzymes, or bilirubin) are not sufficient to

establish a diagnosis of cGVHD. If the liver is the only organ involved (or if there are concurrent acute GVHD features) and a liver biopsy is undertaken that confirms GVHD of the liver, this is not enough to establish a diagnosis of chronic GVHD, as liver biopsy is unable to differentiate acute from chronic GVHD. In this situation, the patient should be considered to have acute GVHD, and a diagnostic cGVHD blood sample should not be drawn. On the other hand, if there are biochemical liver abnormalities in the presence of distinctive cGHVD manifestations and a liver biopsy confirms GVHD, this is enough to confirm a diagnosis of chronic GVHD and a cGVHD blood sample can be drawn.

- Chronic GVHD of the lung can be difficult to diagnose, particularly in young children. Bronchiolitis obliterans (BO) is the only diagnostic manifestation of lung cGVHD as per the NIH consensus criteria. Previous cGVHD criteria required a lung biopsy to establish the diagnosis of BO, however, newer consensus criteria acknowledge a greater role for pulmonary function studies (PFTs), particularly when other diagnostic or distinctive cGVHD manifestations exist. PFTs are strongly encouraged in children of appropriate age where cooperation with PFTs usually occurs (often around 7-8 years of age). If a distinctive manifestation of chronic GVHD is present in another organ system, PFTs alone are able to diagnose pulmonary cGVHD if the following criteria are met: (1) The FEV1 / FVC ratio is <0.7 or the 5th percentile predicted (2) FEV1 <75% predicted with ≥ 10% decline in less than 2-years; and FEV1 does not correct to >75% with use of a bronchodilator (3) absence of infection AND at least one of two criteria, either (1) evidence of air trapping on high resolution CT scan of the chest with inspiratory and expiratory views (or small airway thickening or bronchiectasis) OR (2) evidence of air trapping by PFTs with a residual volume >120% predicted or RV/TLC elevated outside the 90% confidence interval.

- If pulmonary cGVHD is the only manifestation of chronic GVHD in the patient, or if the patient is too young to perform PFTs, then a lung biopsy is required to establish the diagnosis of pulmonary cGVHD (BO).

- The diagnostic chronic GVHD blood sample should be drawn at the earliest time point once the clinical suspicion of chronic GVHD developing has occurred. It is recognized that further investigations may be required after this point. Preference is to draw the cGVHD blood sample before systemic immunosuppression is escalated for a specific diagnosis of chronic GVHD (addition of topical agents such as topical steroids or tacrolimus is allowed). It is recognized that many of these patients will already be on systemic immune suppression, either as part of GVHD prophylaxis or from previous treatment of acute GVHD.

- Each of the major organ systems potentially involved by chronic GVHD should be individually scored (**Appendix X**), regardless of whether or not the organ system is actually involved with cGVHD. The eyes and genitourinary tract should be assessed by a specialist (opthamologist, gynecologist) if concern for cGVHD involvement. Although photographic range of motion of joints (shoulder, elbow, wrist, ankle) is included to aid in the clinical diagnosis of sclerosis, and can be recorded on the severity scoring, the value is not required for the final severity scoring of cGVHD involving the joints / fascia.

- A final overall global severity score of cGVHD score should be assigned at the time of cGVHD diagnosis, according to the final scoring system in Appendix X.

Table 1: Clinical Manifestations of Chronic GVHD According to NIH Consensus Criteria

ORGAN OR SITE	DIAGNOSTIC *(Sufficient to establish the diagnosis of chronic GVHD*	DISTINTIVE* *(Seen in chronic GVHD but insufficient alone to establish a diagnosis)*	OTHER FEATURES OR UNCLASSIFIED ENTITIES**	COMMON *** *(Seen with both acute and chronic GVHD)*
SKIN	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen-sclerosis features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
NAILS		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric, affects most nails)		
SCALP AND BODY HAIR		• New onset of scarring or non-scarring scalp alopecia, (after recovery from chemotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse or dull (not explaned by endocrine or other causes) • Premature gray hair	
MOUTH	• Lichen planus-like changes	• Xerostomia • Mucoceles • Mucosal atrophy • Ulcers • Pseudomembranes		• Gingivitis • Mucositis • Erythema • Pain
EYES		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periobital hyperpigmentation • Blepharitis (erythema of the eye lids with edema)	

ORGAN OR SITE	DIAGNOSTIC *(Sufficient to establish the diagnosis of chronic GVHD*	DISTINTIVE* *(Seen in chronic GVHD but insufficient alone to establish a diagnosis)*	OTHER FEATURES OR UNCLASSIFIED ENTITIES**	COMMON *** *(Seen with both acute and chronic GVHD)*

Genitals	• Lichen planus-like features • Lichen sclerosus-like features	• Erosions • Fissures • Ulcers			
Females	• Vaginal scarring or clitoral/labial agglutination				
Males	• Phimosis or urethral/meatus scarring or stenosis				
GI Tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children)	
Liver				• Total bilirubin alkaline phosphatase > 2x upper limit of normal • ALT > 2x upper limit of normal	
Lung	• Bronchiolitis obliterans diagnosed with lung biospy • Bronchiolitis obliterans syndrom (BOS) ‡	• Air trapping and bronchiectasis on chest CT	• Crytogenic organizing pneumonia (COP) † • Restrictive lung disease†		

ORGAN OR SITE	DIAGNOSTIC *(Sufficient to establish the diagnosis of chronic GVHD*	DISTINTIVE* *(Seen in chronic GVHD but insufficient alone to establish a diagnosis)*	OTHER FEATURES OR UNCLASSIFIED ENTITIES**	COMMON *** *(Seen with both acute and chronic GVHD)*
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis ††	• Edmea • Muscle cramps • Arthralgia or arthritis	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo – or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP) • Raynaud's phenomenon	
Other			• Pericardial or pleural effusion • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthena gravis • Cardiac conduction abnormality or cardiomyopathy	

*In all cases, infection, drug effect, malignancy, or other causes must be excluded.
** Can be acknowledged as part of the chronic GVHD manifestation if diagnosis is confirmed.
*** Common refers to shared features by both acute and chronic GVHD
‡ BOS can be diagnostic for lung chronic GVHD only, if distinctive sign or symptom present in another organ (see text)
† Pulmonary entities under investigation or unclassified
†† Diagnosis of chronic GVHD requires biopsy
Abbreviations: ALT (alanine aminotransferase); PFTs (pulmonary function tests): AIHA (autoimmune hemolytic anemia); ITP (idiopathic thrombocytopenic purpura)

APPENDIX XII: SEVERITY SCORING OF CHRONIC GVHD BY ORGAN SYSTEM AND FINAL cGVHD SCORE

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)

SKIN				
☐ **SCORE % BSA** *GVHD features to be scored by BSA* **Check all that apply:** Maculopapular rash/erythema Lichen planus-like features Sclerotic features Papulosquamous lesions or ichthyosis Keratosis pilaris-like GVHD	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
SKIN FEATURES SCORE:	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** Deep sclerotic features "Hidebound" (unable to pinch) Impaired mobility Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** Hyperpigmentation Hypopigmentation Poikiloderma Severe or generalized pruritus Hair involvement Nail involvement *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
MOUTH Lichen planus-like features present: **Yes** **No** *Abnormality present but explained entirely by non-GVHS documented cause (specify):*_____	No symptoms	Mild symptoms **with** disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs **with** partial limitation or oral intake	Severe symptoms with disease signs on examination **with** major limitation or oral intake

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist: **Yes** **No** **Not examined**	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs) **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
GI TRACT **Check all that apply:** Esophageal web/proximal stricture or ring Dysphagia Anorexia Nausea Vomiting Diarrhea Weight loss ≥ 5%* Failure to thrive	No symptoms	Symptoms without significant weight loss* (<5%)	Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
LIVER	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤ 3 mg/dL or ALT > 5 ULN	Elevated total bilirubin > 3 mg/dL
Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
LUNGS** **Symptom score:**	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score: % FEV1 ☐	FEV1≥80%	FEV1 60-79%	FEV1 40-59%	FEV1≤ 39%
Pulmonary function tests Not preformed Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				

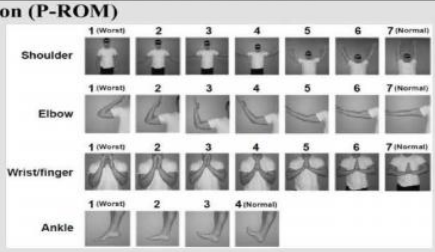
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score (see below) Shoulder (1-7):___ Elbow (1-7):___ Wrist/finger (1-7):___ Ankle (1-4): ____	No symptoms	Mild tightness of arms or legs normal or mild decreaed range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderatedecrease ROM **AND** mild to moderate limitation of ADL	Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
GENITAL TRACT *(See Supplemental figures[†])* Not examined *Currently sexually active* Yes No	No signs	Mild signs[‡] and females with or without discomfort on exam	Moderate signs[‡] and may have symptoms with discomfort on exam	Severe signs[‡] with or without symptoms
Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

Ascites (serositis)___	Myasthenia Gravis___	
Pericardial Effusion___	Peripheral Neuropathy___	Eosinophilia > 500/µl___
Pleural Effusion(s)___	Polymyositis___	Platelets <100,000/µl ___
Nephrotic syndrome___	Weight loss>5%* without GI symptoms ___	Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑ No GVHD ❑ Mild ❑ Moderate ❑ Severe

Photographic Range of Motion (P-ROM)



[†] Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.
*Weight loss within 3 months
** Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible, FEV1 should be used in the final lung scoring where there is a discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (Easter Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area) ; ADL (activities of daily living); LFTs (liver function test); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit)
[ǂ]To be completed by specialist or trained medical providers (see Supplemental Figure)

Mild chronic GVHD

1 or 2 organs involved with no more than score 1 plus
Lung score 0

Moderate chronic GVHD

3 or more organs involved with no more than score 1
OR
At least 1 organ (not lung) with a score of 2
OR
Lung score 1

Severe chronic GVHD

At least 1 organ with a score of 3
OR
Lung score of 2 or 3

Key Points:

1. In skin higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

APPENDIX XIII: MINIMAL RESIDUAL DISEASE TESTING BY Ig/TR CLONALITY (COG SITES)

Background

Multiple studies have demonstrated that minimal residual disease levels (MRD) early in therapy are prognostically important in pediatric B-ALL.[12,13] On the AIEOP-BFM 2000 trial, patients with non-Ph+ B-ALL with high end-IB MRD had the highest risk of treatment failure (hazard ratio 7.51, $p< 0.001$).[3] Results from AIEOP-BFM studies indicate that non-Ph+ ALL patients with high end-IB MRD who have persistent MRD after receiving the 3 Consolidation blocks (identical to those administered on the standard arm of AALL1631) have an extremely high risk of relapse.

Data regarding the prognostic significance of MRD levels at various time points during therapy for Ph+ ALL patients are more limited. Based on the results in Ph-negative B-ALL patients, treatment decision on AALL1631 will be made based on MRD measured from the marrow at two time points:

- End-IB: Patients will be risk stratified based on MRD at this time point (SR: MRD < 5 x 10-4; HR MRD ≥ 5 x 10-4)
- End Consolidation Block 3 (HR patients only): Patients with MRD ≥ 10^{-2} at this time point will be removed from protocol therapy and be considered candidates for alternative therapies.

In addition, we will explore the prognostic significance of MRD at several other time points during therapy, but will not make treatment decisions based on the results. Patients who consent to the optional MRD research study will have marrow samples obtained at the following time points:

- All patients: End of Induction IA
- HR: prior to HSCT, start of post-HSCT imatinib (Day +56), Day +90, Day +180 and Day +365.

MRD will be primarily assessed by the Ig-TR clonality assay at both COG and EsPhALL sites using identical methodology. An alternative Next Generation Sequencing (NGS)/high throughput sequencing approach for MRD detection has been developed and validated.[19,20] On AALL1631, we plan to prospectively evaluate NGS MRD in both SR and HR patients treated at COG sites and compare results obtained with this assay and those from Ig-TR PCR.

Methodology

Ig-TR clonality PCR assay for COG participants will be performed at the COG Leukemia Molecular Reference Laboratory and Biospecimen Bank at Nationwide Children's Hospital (NCH) in Columbus, Ohio, the central testing location for molecular studies for many COG studies including the recent Ph+ ALL study (AALL1122), which utilized the same testing methodology. NGS will be carried out at Adaptive Biotechnologies in Seattle, Washington, in a CLIA-certified laboratory. Dr. Ilan Kirsch, Senior Vice President, Translational Medicine, will provide consulting services.

RQ-PCR Assay: MRD monitoring via immunoglobulin (Ig) and T-cell receptor (TR) gene rearrangements involves four major steps: 1) identification of Ig/TR rearrangements by PCR; 2) homo/heteroduplex analysis to discriminate between PCR products derived from monoclonal (homoduplexes, identical junctional regions) and polyclonal lymphoid cell populations (heteroduplex smear with products having heterogeneous junctional regions); 3) Identification and design of one to two sets of clone-specific

primers (dependent upon number of clones); 4) RQ-PCR for quantification of the patient specific gene rearrangement(s).

DNA will be isolated from bone marrow from each time point using the QIAmp DNA mini kit. Upon hematopathologist review to determine accurate blast percentage, the time point will be simultaneously run with the diagnostic sample to quantify and compare the patient specific Ig/TR clone copy number. To limit the chance of false-negative MRD results due to clonal expansion, two or more PCR targets will be used for each patient (same as integral marker testing for MRD).

Analyses will be performed using the diagnostic sample combined with subsequent time points to quantify MRD. This method has a sensitivity of at least one leukemic cell in a background of 10^{-3} normal cells (typically $1x10^{-5}$).

Primer specificity is first tested by running an RQ-PCR assay with buffy coat (BC) DNA, the patient diagnostic sample, and no template control. In order to determine the sensitivity of the RQ-PCR, a serial dilution of the diagnostic sample is made. The 10^{-1} to 10^{-5} dilutions are analyzed in duplicate along with BC DNA (6 fold) and a single no DNA control. The 5 log steps are based on historical data and agreement within EuroMRD that a theoretical sensitivity of an RQ-PCR assay using the recommended DNA input of 500 ng/reaction (corresponding to approximately $1x10^5$ cells) is 10^{-5}.

A standard curve is generated by serially diluting the diagnostic DNA specimen in DNA from mononuclear cells of a pool of 5-10 healthy donors. The serial dilutions range from 10^{-1} to at least 10^{-5}, and are tested in triplicate. The first dilution step of the diagnostic sample is based on the blast cell percentage determined in exactly the same sample, such that the 10^{-1}sample truly contains 10% blasts. By plotting the log value of this dilution against the threshold or crossing point (C_T), a standard curve is obtained. The standard curve will then be used to compare each of the follow up samples to quantitate residual disease within a given patient.

To determine the background of the RQ-PCR assay (the nonspecific amplification of comparable Ig/TR gene rearrangements present in normal cells), DNA is obtained from MNC from a pool of five to 10 healthy donors. As nonspecific amplification is generally only detected at a low level and outside the quantitative range of the RQ-PCR, nonspecific amplification controls are run at least in ≥6-fold in each RQ-PCR analysis for each Ig or TR marker. The lowest C_T value of these nonspecific amplification controls is specified as the (highest) background level. No template controls are always be included at least in duplicate in each RQ-PCR experiment. Analysis of follow-up samples is performed in triplicate in which all three values are taken into account.

The sensitivity of the RQ-PCR assay is dependent on several factors, including the type of rearrangement, the size of the junctional region and the amount of DNA in each reaction. If a relatively high proportion of leukemic cells are present, the MRD level is reliably quantified in the majority of cases. The sensitivity is the lowest dilution that meets all the following criteria: 1) must give specific amplification, as determined by the shape of the amplification curve; 2) must have at least one positive replicate (ΔC_T of the replicates is not relevant here); 3) must have the lowest C_T value ≥1.0 lower than the lowest C_T value of the background (amplification observed in normal MNC DNA); 4) must have the lowest C_T value <20 cycles from the undiluted sample or, if this undiluted sample is not included in the standard curve, from the intercept of the standard curve (representing the 10^0 dilution). The 20 cycles reflect five log steps in the case of a standard curve with a maximally accepted slope of (-3.9).

Based on the EuroMRD Guidelines (followed in the AALL1122 trial), a sample will be considered MRD positive if: 1) the C_T value of at least one of the three replicates is ≥1.0 C_T lower than the lowest C_T of

background and 2) the C_T value of at least one of the three replicates is within 4.0 C_T of the highest C_T value of the 'sensitivity' (fulfilling all 'sensitivity' criteria). Alternatively, a follow-up sample will be considered 'MRD negative' if: 1) no amplification is observed; 2) the lowest C_T value of the target is within one C_T from the lowest C_T of the background; and 3) all C_T values are more than four cycles separated from the highest C_T value of the 'sensitivity.

Multiplex PCR and High Throughput Sequence Analysis: An aliquot of genomic DNA from each sample will be set aside for comparative testing by standardized multiplex PCR and high-throughput sequencing as performed by the CLIA/Cap certified laboratory of Adaptive Biotechnologies, Seattle, Washington and as previously described. [19,20,82] Routinely 400 ng of genomic DNA/locus analyzed is used for the identification of dominant sequences in the sample of interest and, in general the Ig (V(D)J/ DJ) and TR loci are studied in patients with B-cell precursor ALL. Therefore approximately 1 (one) microgram of genomic DNA should be set aside for this purpose from the initial diagnostic samples. Dominant sequence(s) roughly correlated with the blast count of the diagnostic specimens are defined using the following guidance:

1. >5% of all like sequences for the locus under study
2. >1% of the total nucleated cell number in the diagnostic specimen
3. A discontinuous distribution of clonal sequences (e.g. the dominant sequence must have no more than four sequences found in the next decile of sequence frequency beneath it)
4. > 100 estimated templates for any given dominant sequence

Next-generation sequencing of CDR3 regions of IG and TR will be performed to identify complete VDJ/DJ and VJ rearrangements. The sequences for these will be delineated according to the definition established by the International ImMunoGeneTics collaboration. Standard bioinformatic algorithms will be used to identify which V, D, and J segments contributed to each IGH CDR3 sequence and which V and J segments contributed to each TCRG CDR3 sequence. Corresponding post-treatment MRD samples will be sequenced and pretreatment clonal sequences will be searched for the clonal CDR3 sequences that identically matched the clonal sequence derived from analysis of paired, pre-treatment samples, requiring an exact 60 base pair match. Both the presence and the frequency of the MRD clone relative to the total Ig or TR repertoire will be noted. Once the dominant sequence(s) is identified it is available for tracking in subsequent samples from the same patient. Upon receipt of genomic DNA extracted from a subsequent bone marrow sample from any given patient for whom a dominant sequence(s) has been identified a complete repertoire of the Ig and or TR is performed but, in addition, the specific sequence(s) previously identified in the diagnostic specimen is specifically searched for and quantitated.

Required Samples
For each MRD time point, 3-6 mL of marrow should be obtained in a purple top (EDTA) tube.

Reporting of Results
MRD results obtained via the Ig-TR PCR assay at end-IB (all patients) and end of Consolidation Block 3 (HR patients only) will be reported back to participating institutions/physicians as they will be used for clinical decision-making. The MRD results from all other time points will not be reported back to the participating institution or physician as they are for investigative purposes only.

APPENDIX XIV: p190/p210 *BCR/ABL1* BREAKPOINT FUSION TRANSCRIPT ASSAY

Background

The t(9;22) results in a chimeric BCR-ABL1 fusion mRNA and protein in which the amino terminal portion of the ABL1 protein is replaced by *BCR* sequences. While the t(9;22) appears similar at the cytogenetic level in CML, ALL and AML, there is extensive molecular genetic heterogeneity in *BCR-ABL1* fusions. Except in rare cases, the *ABL1* breakpoint is constant and occurs in intron 1, fusing exon 2 of *ABL1* to various portions of the *BCR* gene. In contrast, there are two major breakpoints in the *BCR* gene: the major breakpoint cluster region primarily observed in CML) and the minor breakpoint cluster region (primarily observed in de novo Ph+ ALL). Three different *BCR-ABL1* fusion mRNAs and proteins have been observed:

1. CML4 (p210, b2a2): 210kDa BCR-ABL1 fusion protein resulting from fusion of M-bcr exon 13 (b2) of *BCR* with *ABL* exon 2 (a2).
2. CML3 (p210 b3a2): 210 kDa BCR-ABL1 fusion protein resulting from fusion of M-bcr exon 14 (b3) of *BCR* with *ABL* exon 2 (a2).
3. ALL (p190 e1a2): 190kDa BCR-ABL1 fusion protein resulting from fusion of m-bcr exon 1 (e1) of *BCR* with *ABL* exon 2 (a2).

The p190 form of BCR/ABL1 is commonly found in Ph+ ALL, but also has been observed in CML. Conversely, the p210 form of BCR/ABL1 is most often seen in patients with CML, although can be present in patients with de novo Ph+ ALL. It is possible that some of the de novo Ph+ ALL cases with p210 isoform may be CML presenting in blast crisis.

Previous reports indicate that 10-15% of pediatric Ph+ ALL patients have the p210 isoform. The prognostic significance of the p210 transcript has not been previously evaluated in pediatric Ph+ ALL, and there are only limited available data from adult Ph+ ALL (in patients not treated with TKI) suggesting that this variant may be associated with an inferior prognosis.

Methodology

Detection of the *BCR-ABL1* fusion gene isoform by RT-PCR is the most precise way to identify the different fusion variants. This assay will be performed using banked diagnostic samples from patients who consent to this research testing. The assay for COG samples will be performed at the COG ALL Molecular Reference Laboratory and Biospecimen Bank at Nationwide Children's Hospital (NCH) in Columbus, Ohio.

Following RNA isolation and reverse transcription, the resulting cDNA is amplified using three primer sets. PCR products are analyzed on an Agilent 2100 Bioanalyzer using a DNA Labchip 1000 kit. Positive products are loaded on a 1.5% agarose gel, transferred to a nylon membrane and hybridized with a series of junction probes that detect the b2a2(CML4), b3a2(CML3) or e1a2(ALL) fusions. Controls for each assay include amplification of E2A for RNA integrity, control samples with known *BCR-ABL1* fusions (SUPB-15 for ALL; K562 for CML3; BV-173 for CML4) and a no template control.

The amplification of the E2A internal control must be successful to allow for interpretation of results. A fluorescence of over 150 on Agilent is needed for successful E2A amplification. Likewise, the positive controls (SUPB-15, K562 and BV-173 cell lines) must also amplify successfully and have a similar fluorescence reading. To be positive for the t(9; 22), *BCR-ABL1* products must be of increased fluorescence intensity than the size controls. Assay sensitivity for the fusion is approximately 1-100 cells.

If the E2A control does not amplify, the sample is either an insufficient sample or a sample of poor quality. If positive controls do not amplify, this indicates a PCR run failure. If the negative control cell line or no template amplifies, this indicates a contamination issue. In all cases the assay will be repeated for a particular patient. A positive result is indicated by a band of predicted size that hybridizes to a junction-specific probe.

Required Samples
Testing will be performed from previously banked diagnostic marrow or peripheral blood specimens. No additional sample is required for this testing.

Reporting of Results
The results of *BCR-ABL1* isoform assay will not be reported back to the participating institution or physician. This assay is for investigative purposes only.

APPENDIX XV: *IKZF1* GENE DELETION AND MUTATION STATUS

Background

The transcription factor IKAROS, encoded by the *IKZF1* gene, plays a fundamental role in the developing B and T lymphocytes, natural killer, dendritic cells, and stem cells. The *IKZF1* gene has six zinc fingers of which four are within the N-terminus and are necessary for DNA binding, while those in the C-terminus assist in IKAROS self dimerization as well as dimerization with other IKAROS members. Alternative transcripts of *IKZF1* have been observed in both normal hematopoietic cells and leukemic blast cells. Past studies have shown that alterations of the *IKZF1* gene are present in a significant proportion of childhood and adult ALL having a t(9;22)(q34;q11) rearrangement (Philadelphia chromosome, Ph+), and in cases of chronic myelogenous leukemia (CML) progression to blast crisis.

Several studies have indicated that *IKZF1* deletions are associated with inferior outcomes in pediatric Ph+ ALL [80, 83,84,85,86,87]. There are only limited data regarding the prognostic significance of *IKZF1* gene aberrations in pediatric Ph+ ALL. The purpose of this assay is to determine the frequency of *IKZF1* deletions and sequence variants observed in Ph+ patients in order to determine whether *IKZF1* status is correlated with outcome (disease-free survival).

Methodology

Two assays, array CGH (to detect gene deletions and copy number variants) and Sanger sequencing (to detect missense, frameshift, and splice-site mutations), will be utilized to screen for *IKZF1* deletions and mutations from banked diagnostic specimens in patients who consent to this optional research study. The assays will be performed at the COG ALL Molecular Reference Laboratory and Biospecimen Bank at Nationwide Children's Hospital (NCH) in Columbus, Ohio.

IKZF1 Gene Sequencing

Previous studies of whole gene sequencing analysis in ALL patients have demonstrated that sequence variants in *IKZF1* occur throughout the gene. Therefore, the analysis to be performed on AALL1631 will focus on full gene coding region of *IKZF1* (exons 2-8). Each exon will be amplified using the polymerase chain reaction (PCR) with primers designed to sequence into the surrounding introns to include the splice junctions. The resulting PCR products will be purified and sequenced using M13 primers. These primers have been tested to robustly sequence the coding regions of each gene. The primers will provide coverage of the entire coding region(s) of each targeted exon from both the forward and reverse directions. This coverage is necessary to confirm the presence of heterozygous change where a different base is present on each allele, and the PCR product represents a mix of the two alleles.

Sequencing is considered the "gold standard" of DNA mutation analysis because it provides the best chance of detecting every mutation present in the region analyzed. Sequencing methodology will detect missense, frameshift, and splice-site mutations that may be missed by array CGH. Sequencing methods will not detect large (≥ 1 exon) deletions, duplications, or mutations in regulatory elements associated with *IKZF1*.

Sequencing will be performed using the Sanger method, which allows for the incorporation of chain terminating dideoxy-nucleotides. We will utilize cycle sequencing using Big Dye Terminator sequencing kits from Applied Biosystems. The sequencing products will be separated on an ABI Genetics Analyzer 3130xl and/or 3730 which detect the fluorescently labeled dideoxynucleotides by laser. The resulting sequences will be aligned using Sequencher software (GeneCodes, Inc.) and/or Mutation Surveyor

(SoftGenetics, Inc.) and compared to the published sequence of *IKZF1* to identify mutations and/or polymorphisms.

All changes identified in clinical sequence analyses will first be compared to our internal *IKZF1* variant table summarizing all previously reported known mutations and polymorphisms. An "up to date," peer-reviewed literature search will be carried out to ensure accurate reporting of identified sequence changes. If a novel sequence change is identified, it will be reported as a variant of unknown significance, with an explanation of our best determination of the nature of the change based on its conservation across species (SIFT: http://blocks.fhcrc.org/sift/SIFT.html), mutation-prediction program (PolyPhen: http://genetics.bwh.harvard.edu/pph/), splice site prediction (when applicable, Berkeley Drosophila Genome Project: http://www.fruitfly.org/seq_tools/splice.html; human), and the type of amino acid substitution (polar vs non-polar, for example).

Diagnostic specimens will be captured as negative for pathogenic variants, heterozygous for a pathogenic or likely pathogenic variant, or heterozygous/homozygous for a variant of unknown significance (VUS). Known polymorphisms (benign sequence changes) will also be documented. Previous studies indicated that that a minimum of 40% blasts will be required to identify *IKZF1* variants within a mixed cell population; therefore, a minimum of 40% blasts will be required to determine a negative result.

Array CGH
The use of genomic microarray technology in detecting differences in germline DNA versus somatic changes in hematological malignancies for prognostic value has now been recognized. Differential labelling of test and reference DNA by competition and imbalances due to copy number differences results in a shift in fluorescence spectra. In array CGH (aGGH), the relative hybridization intensity of the test and reference signals at a given location is proportional to the relative copy number of those sequences in the test and reference genomes. When the reference sample used is normal, any increases or decreases in signal intensity ratios directly indicate DNA copy number differences within the genome of the test cells. The data is typically normalized so that the modal ratio for the genome is set to a standard value. CGH microarrays that utilize oligonucleotides (oligos) for all or parts of the human genome are currently available commercially. The use of oligos with known map positions allows direct correlation of DNA copy number gains and losses with specific genomic sequence. This difference in signal intensity has been shown to be a reliable indicator for assessing gene copy number within a mixture of clone populations.

A targeted high-density oligonucleotide array for the *IKZF1* gene region (Agilent Technologies, Inc., Santa Clara, CA) using UCSC human genome Mar 2006/NCBI36/hg18 build (http://genome.ucsc.edu/cgi-bin/hgGateway) has been previously designed and will be utilized for AALL1631 to determine copy number variations of *IKZF1*. The custom designed, high-density, 8 × 15k array format was enhanced and targeted for regions within and flanking the entire *IKZF1* gene. The probes were constructed to allow for genomic tiling with an average probe spacing of 20 bp and a probe length of 50 bp. The probe coverage included 5,000 bp 5' and 3' of the *IZKF1* gene, with a total of 1,492 probes within the region. The custom oligonucleotide array is designed to detect both focal (≥ 1 exon) and broad deletions or duplications in *IKZF1*.

The sequencing and array methods described herein were previously used to report on the frequency of *IKZF1* alterations in 1061 pediatric and adolescent B-precursor ALL patients from previous COG Trials, P9905 and P9906.[83]

APPENDIX XVI: FLUORESCENCE IN SITU HYBRIDIZATION (FISH) LABORATORY FORMS FOR CENTRAL REVIEW OF BCR-ABL1 FUSION DETERMINATION

For COG sites only.

APPENDIX XVII: EsPhALL2017/COGAALL1631 DSMC CHARTER

EsPhALL2017/COGAALL1631

Data and Safety Monitoring Committee Charter

Date 5th April 2017 - Version: 1.0

EudraCT No.: 2017-000705-20

CONTENT	COMMENTS
1. Introduction	
Objectives of trial, including interventions being investigated	Please refer to the trial synopsis.
Outline of scope of Charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the independent Data Safety and Monitoring Committee (DSMC) for the EsPhALL2017/COGAALL1631 trial, including the timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, statistical issues and relationships with other committees.
2. Roles and responsibilities	
A broad statement of the aims of the committee	To safeguard the interests of participants, assess the safety and efficacy of the interventions, and monitor the overall conduct of the clinical trial.
Terms of reference	The DSMC should review the progress and accruing data of the trial and provide recommendations about whether the study needs to be changed or terminated based on interim analyses. The DSMC also determines whether and to whom outcome results should be released prior to the reporting of study results at the time specified in the protocol.
Specific roles of DSMC	Interim review of the trial's progress including updated figures on recruitment, data quality, main outcomes and safety data. Specific aspects include: • Monitor recruitment • Assess data quality, including completeness (and by so doing encourage collection of high quality data) • Monitor compliance with the protocol • Monitor evidence for treatment differences in the main efficacy outcome measures • Monitor evidence for treatment harm (e.g. toxicity data, Serious Adverse Events, deaths) • Decide whether to recommend that the trial

	continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups • Suggest additional data analyses • Advise on protocol modifications suggested by investigators or sponsors (e.g. to inclusion criteria, trial endpoints or sample size) • Monitor planned sample size assumptions • Monitor compliance with previous DSMC recommendations • Consider the ethical implications of any recommendations made by the DSMC • Assess the impact and relevance of external evidence
Relationship with the Sponsor	DSMC member will interact with a Sponsor designee (Giuseppe Dastoli, MD).
3. Trial implementation	
Whether the DSMC will have input into the protocol	DSMC members will be sent a copy of the protocol. This will have undergone review by the Sponsor and the protocol concept approved and peer-reviewed by the contact person of each national participating group. Therefore DSMC members will have no direct input into the trial design. Hence, if a potential DSMC member has reservations about the trial, they should report these to the Sponsor designee and may, at their discretion, choose not to accept the invitation to join the DSMC. DSMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Any issues specific to the disease under study	EsPhALL2017/COGAALL1631 involves paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL) which is a rare disease. The trial will recruit from 18 countries in the EsPhALL network and from North America (COG) and is expected to recruit to time and target. However, recruitment may have to be carefully monitored throughout the trial to avoid

	delays.
Any specific regulatory issues	There are no specific regulatory issues
Whether members of the DSMC will have a contract	Members of the DSMC will not formally sign a contract but should formally register their assent to join the committee by signing the signature page at the end of this Charter. By signing, they confirm that they agree to join the DSMC, agree to treat all trial data and discussions confidentially, agree with the contents of the Charter, and agree to follow the instructions as captured in the Charter. Please Note: Any competing interests should also be declared on the signature page.
4. Composition	
Membership and size of the DSMC	The proposed members of the DSMC for this trial are: 1. Professor Oliver Ottmann, Professor of Haematology, Clinician 2. Dr. Alessandro Rambaldi, Head of Hemato-oncology Dept., Clinician 3. Member of COG DSMC (to be named) 4. Dr. Simona Iacobelli, Assistant Professor in Medical Statistics, Statistician Members will be asked to provide the Sponsor designee with a short CV including details of their clinical trials experience.
The DSMC Chair, how s/he is chosen and the Chair's role	The nominated DSMC Chair will have previous experience of serving on DSMCs and will be able to facilitate and summarize discussions. The Chair will be nominated by the Sponsor designee in agreement with the DSMC members.
The responsibilities of the DSMC statistician	The DSMC membership will include a statistician to provide independent statistical expertise.

The responsibilities of the Trial Statistician	The Trial Statistician will produce (or oversee the production of) an Open and Closed DSMC Report and will participate in DSMC meetings, guiding the DSMC through the report, participating in DSMC discussions and taking notes.
The responsibilities of the Study Chairs and other members of the Study Team	The Study Chairs and members of the Study Team will help the Trial Statistician to produce the Open DSMC Report. They will attend open sessions of the meeting. They will assure that DSMC is advised about relevant non-confidential results from other related studies as they become available.
5. Relationship	
Relationships with Study Chairs, Study Team and other trial committees (e.g. Study Steering Committee (SSC))	A list of the individuals and groups (with abbreviations) involved in study oversight, along with their responsibilities, is provided in Table 1 at the end of this document.
Clarification of whether the DSMC are advisory (make recommendations) or executive (make decisions)	The DSMC has an advisory role, and will make comments, requests and recommendations to the Sponsor designee.
Payments to DSMC members	Members will be reimbursed for reasonable travel and accommodation costs when face-to-face meetings occur. No other payments or rewards are given.
The need for DSMC members to disclose information about any competing interests	Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. DSMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
6. Organization of DSMC meetings	
Expected frequency of DSMC meetings	The DSMC will meet at least twice per year during the recruitment phase, and more frequently if deemed necessary.

Whether meetings will be face-to-face or by teleconference	It is anticipated that, due to the frequency of meetings, they will routinely be held via teleconference. Face-to-face meetings will be organized if deemed necessary by DSMC.
How DSMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	A mixture of open and closed sessions will be held. Only DSMC members, the Trial Statistician and his/her collaborators in the production of the DSMC Reports will be present in closed sessions. In open sessions, all those attending the closed session are joined by the Study Chairs, and where possible by relevant members of the ST. The format of the meetings will be based on the following structure. 1. Open session: Introduction, discussion of Open DSMC Report 2. Open session: DSMC conclusions 3. Closed session: DSMC discussion of Closed DSMC Report 4. Closed session: DSMC deliberation and conclusions
7. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Accumulating information relating to recruitment, data quality (e.g. data return rates) and toxicity details based on pooled data will be presented.
Intended content of material to be available in closed sessions	In addition to all the material available in the open session, the closed session material will include efficacy and safety data by treatment group.
Will the DSMC be blinded to the treatment allocation?	Interim analyses will be submitted blinded (or unblinded, if specifically requested by the DSMC).
Who will see the accumulating data and interim analysis for closed sessions?	The accumulating data and interim analysis will be seen by the DSMC members and the Trial Statistician. The Study chairs and SSC will not have access to these reports. DSMC members must not share confidential information with anyone outside the DSMC, including the Study Chairs.

Who will be responsible for identifying and circulating external evidence (e.g. from other trials/ systematic reviews)?	Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the DSMC members. The ST will collate any such information for presentation in an open session.
Whether reports to the DSMC be available before the meeting or only at/during the meeting	The DSMC Reports (Open and Closed) will be circulated to DSMC members at least a week prior to the meeting.
To whom the DSMC will communicate the decisions/ recommendations that are reached	The DSMC will communicate its formal recommendations to the sponsor designee. The formal recommendations should include a statement suitable for circulation to other parties (eg, SSC) indicating whether the trial may continue as planned or if any changes are recommended.
What will happen to the confidential reports after the meeting?	The DSMC members should store the report in a secure location after each meeting so they may check the next report against them. After the trial is reported, the DSMC members should destroy all interim reports.
8. Decision making	
What decisions/ recommendations will be open to the DSMC?	Possible recommendations from the DSMC include: • No action needed, trial continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence • Stopping recruitment within a subgroup • Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up • Sanctioning and/or proposing changes to trial design

How decisions or recommendations will be reached within the DSMC	The Chair is to summarize discussions and encourage consensus. Every effort should be made for the DSMC to reach a unanimous decision. If the DSMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the DSMC Response Report as this may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial be considered before any recommendation is made.
When the DSMC is quorate for decision-making	Effort should be made for all members to attend. If, at short notice, any DSMC members cannot attend, the DSMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DSMC is considering recommending major action after such a meeting the DSMC Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further meeting should be arranged with the full DSMC.
What happens to members who do not attend meetings	DSMC members who will not be able to attend the meeting may pass comments to the DSMC Chair for consideration during the discussions. If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they will be asked if they wish to remain part of the DSMC. If a member does not attend a third meeting, they may be replaced.
9. Reporting	
Role of Sponsor (Designee)	Upon receipt of DSMC recommendations, the Sponsor designee will share recommendation with COG Group Chair and Study Chairs. In the event that the DSMC recommends a study change for patient safety reasons (including early stopping), the sponsor will act to implement the change as expeditiously as possible.

	If a change is recommended by DSMC, the Trial Statistician may send the written report that was prepared prior to DSMC meeting to the Sponsor designee, who may seek the advice, in a confidential manner, of the COG Group Chair and Study Chairs.
What will be done if there is disagreement between the DSMC and the body to which it reports	The trial sponsor has ultimate responsibility for the trial and assumes primacy. If the sponsor does not concur with the DMSC recommendation, the sponsor must inform the DSMC Chair, providing details as to how the DSMC's recommendations will be acted upon. If the DSMC has serious problems or concerns with the sponsor decision, a meeting of these groups should be held. Depending on the reason for the disagreement, confidential data may have to be revealed to all those attending such a meeting.
10. After the trial	
Publication of results	The DSMC would usually cease its involvement after patient recruitment and treatment is complete. However, it may request to stay involved for longer, for example until publication. Depending on the results of the trial and the ease of their interpretation, at the end of the trial there may be a meeting to allow the DSMC to discuss the final data with the ST to give advice about data interpretation. The main trial results will be published in a correct and timely manner. The SSC should oversee this process. DSMC members will be named and their affiliations listed in the main trial report, unless they explicitly request otherwise.
Any constraints on DSMC members divulging information about their deliberations after the trial has been published	The DSMC members should not discuss issues relating to their involvement in the trial until 12 months after the primary trial results have been published, or when permission is agreed with the ST.

Table 1: Structure for Study Oversight

Term	Abbreviation	Description
Study Sponsor		The University of Milano-Bicocca is the overall sponsor of trial. The Chair of the EsPhALL group is Andrea Biondi, who is serving as the EsPhALL study chair for this trial. Therefore the sponsor will appoint a designee, not involved in the study, to whom the DSMC will report for this trial.
Study Team	**ST**	The Study Team will ensure that the study is appropriately conducted with respect to operations, quality and safety according to the protocol provisions. Membership includes the Study Chairs and Vice-Chairs, and the staff of the following units indicated in the protocol: • Study Coordination and Data Center • Clinical Coordination • Central Pharmacovigilance Unit
Data and Safety Monitoring Committee	**DSMC**	An independent committee composed of experienced researchers not involved in the trial (including one statistician) that will be responsible for providing the ST with guidance on the trial conduct, for monitoring the progress of the study on ethic and scientific grounds and to recommend to the ST whether to continue, modify or stop the trial.
Study Steering Committee	**SSC**	The SSC is composed by the national contact persons of cooperative groups participating in the study. The SSC is chaired by the Study Chairs and the Study Vice-Chairs. The SSC will advise on the conduct of the study, will review the study progress, consider feedback from the DSMC and be involved in deciding whether the trial should be stopped, modified or continued.

Possible competing interests, including professional interest, proprietary interest and miscellaneous interest considerations should be disclosed. Examples of potential interests that might compete are listed below, taking into account that no commercial company is involved in the EsPhALL2017/COGAALL1631 study. In many cases, simple disclosure up front should be sufficient. Otherwise, the (potential) DSMC member should remove the conflict or stop participating in the DSMC. Depending on the nature of the interest, this will not necessarily exclude you from membership.

Potential competing interests:

- Consulting arrangements with the Sponsor or their representative
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in one of the trial's arms
- Involvement in regulatory issues relevant to the trial
- Investment (financial or intellectual) or career tied up in competing products

NO, I have no competing interests to declare ☐

YES, I have competing interests to declare (please, provide details below) ☐

_____

_____

_____

Tick to agree

I have read, understood and agree with EsPhALL2017/COGAALL1631 DSMC Charter version 1.0, dated 4th April 2017 ☐

I agree to join the independent Data and Safety Monitoring Committee for this trial ☐

I agree to treat all trial documentation, data and discussions confidentially ☐

Print name: _____

Signature: _____ Date: ____/ _____/ _____
DD MM YYYY

APPENDIX XVIII: EsPhALL2017/COGAALL1631 STUDY SYNOPSIS

Title	International phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones
Subjects	Patients with newly diagnosed ALL (B-ALL or T-ALL) with definitive evidence of BCR-ABL1 fusion aged > 1 year and ≤ 21 years.
Stratification	MRD results at end of Induction IB will be used to risk-stratify patients as follows: Standard risk (SR): MRD < 5 x 10^{-4} High risk (HR): MRD ≥ 5 x 10^{-4} MRD will be assessed by RQ-PCR of rearranged immunoglobulin/T-cell receptor genes (IgH/TCR). For patients with uninformative IgH/TCR rearrangements, MRD will be assessed by flow cytometry (in such a case the values defining SR will be < 0.05% and HR will be ≥ 0.05%).
Primary aim	To compare disease-free survival (DFS) of Standard Risk (SR) Ph+ ALL patients treated with continuous imatinib combined with either the EsPhALL chemotherapy backbone (Arm A) or a less intensive a high-risk COG ALL chemotherapy backbone (Arm B), according to the randomization result. A non-inferiority design will be applied in order to evaluate whether there is significant erosion in DFS in SR patients treated with the less intensive Arm B compared with Arm A.
Secondary aims	1. To determine the feasibility of administration of imatinib after allogeneic HSCT in High Risk (HR) Ph+ ALL patients. 2. To determine event-free-survival (EFS) of HR pediatric Ph+ ALL patients treated with EsPhALL chemotherapy, HSCT in first complete remission and post-HSCT imatinib. 3. To compare rates of Grade 3 or higher infections in SR Ph+ ALL patients between the two randomized arms. 4. To evaluate EFS and overall survival (OS) of all enrolled participants. 5. To evaluate OS in SR patients. 6. To evaluate OS in HR patients.
Primary endpoint	DFS, defined as the time from randomization to first event (relapse, second malignancy, or death in complete remission) or time to last follow-up for patients without events.
Secondary endpoints	1. Feasibility of post-HSCT imatinib is defined as the proportion of patients who receive at least 75% of intended doses. 2. EFS is defined as the time from the date of bone marrow for MRD assessment at end-IB to first event [resistant disease (MRD ≥ 10^{-2} or morphologic residual disease at end of Consolidation Block 3), relapse, progressive disease (i.e. MRD ≥ 10^{-2} at two post-HSCT time points separated by at least 2 weeks obtained at Day 90 or later from HSCT), second malignancy, or death in complete remission] or time to last follow-up for patients without events. 3. Rates of Grade 3 or higher infections according to CTCAE, Version 4.0, in SR patients in both randomized arms. 4. EFS (defined as time from enrollment until the first occurrence of: M3 marrow at the end of Induction IA, relapse, second malignancy, or death as a first event) and OS defined as the time from study enrollment to death from any cause. 5. OS, defined as the time from randomization to death from any cause. 6. OS, defined as the time from MRD assessment at end-IB to death from any cause.

Study design	International, multicenter, randomized, non-inferiority, phase 3 study
Participating Countries/Groups	• EsPhALL network: AIEOP (Italy), BFM (Austria), BFM (Germany and Switzerland), COALL (Germany), CPH (Czech Republic), DCOG (the Netherlands), FRALLE (France), NOPHO (Denmark, Finland, Lithuania, Norway, Sweden), NCRI (United Kingdom), PINDA (Chile), HKPHOSG (Hong-Kong), ANZCHOG (Australia, New Zealand), INS (Israel), Slovakia, PPLLSG (Poland). • COG (USA, Canada)
Study population	The trial will enroll a maximum of 700 subjects at COG and EsPhALL sites (approximately 120 per year). The target for the randomized study in SR is N=475 eligible and evaluable patients, while in the HR stratum 90-120 patients are expected. Accrual will close upon enrolling 475 randomized SR patients.
Study duration	Expected enrollment period is 6 years and minimum follow-up is 3 years.
Eligibility criteria	1. Patients should be previously enrolled on the National ALL front-line protocol. For patients who were not, baseline BM diagnostic samples must be available. 2. Age > 1 year and ≤ 21 years at ALL diagnosis. 3. Newly diagnosed ALL (B-ALL or T-ALL) with definitive evidence of BCR-ABL1 fusion by karyotype, FISH and/or RT-PCR. 4. Previous start of Induction therapy which includes vincristine, a corticosteroid, usually PEG-L-Asparaginase, with or without anthracycline, and/or other standard cytotoxic chemotherapy. 5. Administration of no more than 14 days of multiagent Induction therapy beginning with the first dose of vincristine. 6. Administration of no more than 14 days of imatinib. 7. Performance status corresponding to ECOG scores of 0, 1, or 2. 8. Adequate liver function. 9. Adequate cardiac function. 10. Adequate renal function.
Exclusion criteria	1. Known history of chronic myelogenous leukemia (CML). 2. ALL developing after a previous cancer treated with cytotoxic chemotherapy. 3. Active, uncontrolled infection or active systemic illness that requires ongoing vasopressor support or mechanical ventilation. 4. Down syndrome. 5. Pregnancy. 6. Breast feeding. 7. Patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation. 8. Patients with congenital long QT syndrome, history of ventricular arrhythmias or heart block. 9. Prior treatment with dasatinib, or any BCR-ABL1 inhibitor other than imatinib.

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