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CHILDREN'S ONCOLOGY GROUP

AALL0631

A Phase III Study of Risk Directed Therapy for Infants with Acute Lymphoblastic Leukemia (ALL): Randomization of Highest Risk Infants to Intensive Chemotherapy ± FLT3 Inhibition (CEP-701, Lestaurtinib; IND#76431; NSC#617807)

A Groupwide Phase III Study

IND Sponsor: COG

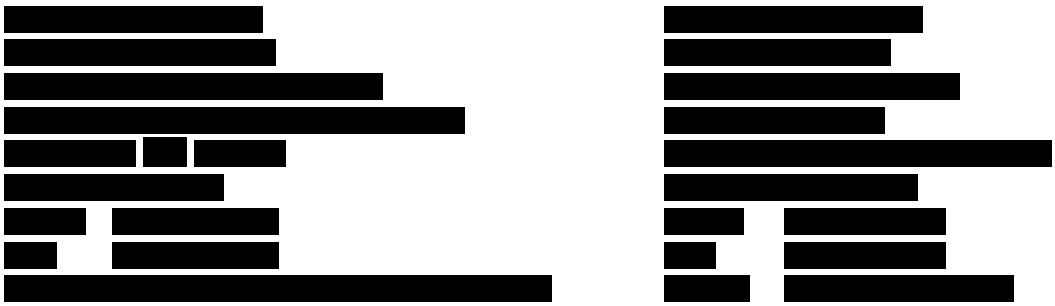

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TABLE OF CONTENTS

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SEE SECTION 13 FOR SPECIMEN SHIPPING ADDRESSES

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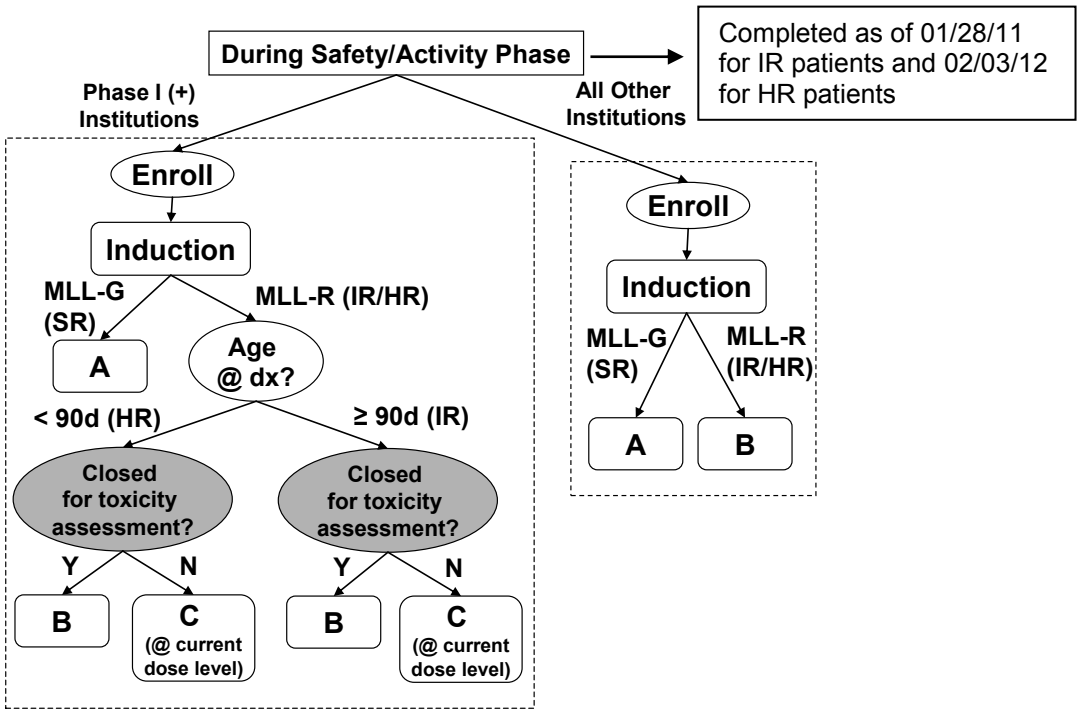
ABSTRACT

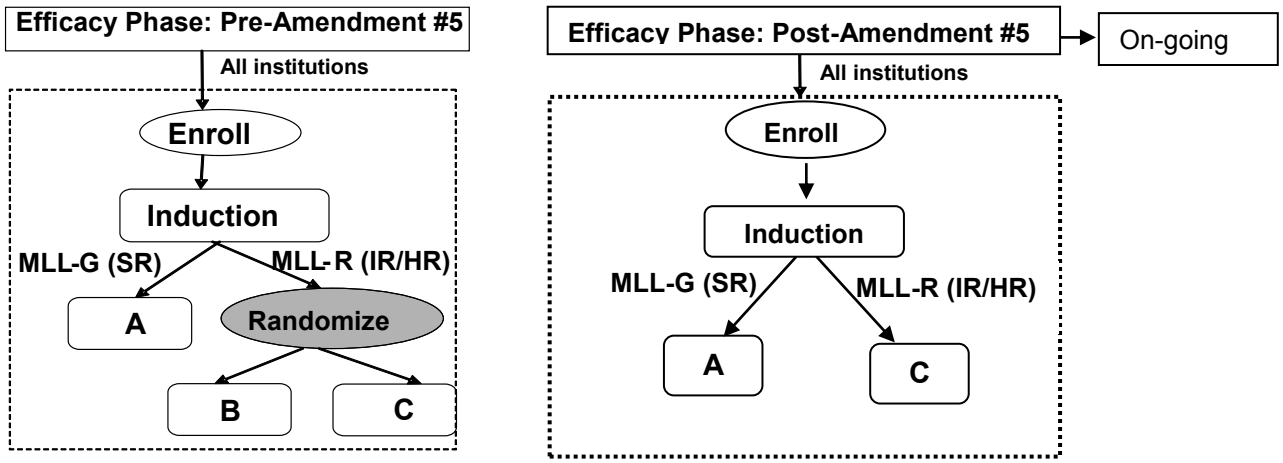
Infants with acute lymphoblastic leukemia (ALL), and in particular those with mixed lineage leukemia (MLL) gene rearrangement, have experienced poor outcomes. Results from Children's Oncology Group (COG) study P9407 suggest that attempts to intensify chemotherapeutics have reached the limits of acceptable toxicity, and that hematopoeitic stem cell transplantation does not improve outcome for these patients. Thus, novel treatment approaches are required.

The FLT3 kinase has been shown to be consistently highly expressed and activated in MLL-R ALL. FLT3 inhibitors, such as lestaurtinib (CEP-701), selectively kill MLL-R ALL cells *in vitro* and *in vivo*, and synergize with chemotherapy. Lestaurtinib is in clinical development for adult and pediatric AML.

This study will be done in two phases: a safety/activity phase, which will determine the dose of lestaurtinib that, in combination with P9407-based chemotherapy, is safe, tolerable and biologically active in infants with MLL-R ALL; and an efficacy phase, in which infants with MLL-R ALL will receive the modified chemotherapy regimen with the incorporation of lestaurtinib. Infants with MLL-G ALL will be non-randomly assigned to receive a less intensive chemotherapy regimen without lestaurtinib.

EXPERIMENTAL DESIGN SCHEMA





MLL	**-**	***Mixed lineage leukemia* gene**
MLL-G	**-**	**MLL Germline (non-rearranged)**
MLL-R	**-**	**MLL Rearranged**
SR	**-**	**Standard Risk**
IR	**-**	**Intermediate Risk**
HR	**-**	**High Risk**
A	**-**	**Post-Induction Arm A (SR chemo)**
B	**-**	**Post-Induction Arm B (IR/HR chemo)**
C	**-**	**Post-Induction Arm C (IR/HR chemo + lestaurtinib)**

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1 To estimate the 3-year event-free survival (EFS) of infants with MLL-R ALL treated with chemotherapy plus the FLT3 inhibitor lestaurtinib.

1.2 Secondary Objectives

1.2.1 To compare the 3-year EFS of infants with MLL-R ALL treated with chemotherapy plus the FLT3 inhibitor lestaurtinib to MLL-R patients treated with chemotherapy alone.

1.2.2 To determine a safe, tolerable and biologically active dose of lestaurtinib given in sequential combination with chemotherapy in MLL-R infants.

1.2.3 To characterize the pharmacokinetics and pharmacodynamics of lestaurtinib in infants when given at the proposed dose in sequential combination with chemotherapy.

1.2.4 To identify molecular mechanisms of resistance to lestaurtinib in leukemic blasts.

1.2.5 To describe levels of minimal residual disease in infants with ALL within the context of the proposed therapy, and correlate with outcome.

1.2.6 To identify gene expression patterns in diagnostic infant leukemia samples that correlate with outcome within the context of the proposed therapy.

1.2.7 To describe the outcome of infants with MLL-G ALL treated with a modified P9407 chemotherapy backbone that includes an extended Continuation phase.

2.0 BACKGROUND

2.1 Importance of this Study

This trial will test a novel therapeutic intervention that may improve outcome for one of the highest risk groups in pediatric oncology -- infants with MLL gene rearrangements. The specific intervention (FLT3 inhibition) is based on a strong biological rationale with supporting pre-clinical evaluation.

2.2 Risk Stratification in Infant ALL

Infants with ALL have experienced poor event-free survival (EFS), particularly in MLL-rearranged disease. International published results show 22% to 43% 3- to 6-year EFS.[1-6] Historically, the high failure rate in infant ALL has been due to recurrent disease, particularly early relapse < 6-12 months post diagnosis.[1,4,5] Thus, therapeutic efforts in COG for infant ALL have centered on providing shortened, intensified therapy including early Induction Intensification and elimination of age-related dose reductions typical of infant therapy in the past. Compared to prior studies, POG 9407 (Cohorts 1 and 2) and CCG 1953 (concurrent infant ALL studies in the former POG and CCG) significantly reduced early relapse. However, the toxic death rate during Induction exceeded historical controls. As a result, the successor study COG P9407 (Cohort 3) was modified by substituting prednisone for dexamethasone during Induction, and decreasing dose intensity of anthracyclines, successfully reducing Induction toxicity from 17 Induction toxic deaths in 68 patients in POG 9407 (Cohorts 1 and 2) to 8 Induction toxic deaths in 141 patients in COG P9407 (Cohort 3).

Results of POG 9407 (Cohorts 1 and 2) and COG P9407 (Cohort 3) have been used to define risk groups and provide the chemotherapy backbone to be used in this protocol:

	3-year EFS (n)	
	Cohorts 1+2	Cohort 3
All patients	50% (68)	45% (141)
MLL-R	40% (48)	38% (100)
MLL-G	81% (16)	74% (35)
0-90 days	18% (17)	15% (27)
91+ days	61% (51)	52% (114)
91+ days (MLL-R only)	53% (34)	47% (78)

In POG 9407 (Cohorts 1 and 2), age greater or less than 90 days at diagnosis was the most important prognostic factor. The presence of a MLL rearrangement was also prognostic. Preliminary data suggests age </> 90 days at diagnosis and MLL rearrangement status continue to be important prognostic factors in Cohort 3.

The CCG-1953 infant ALL study ran concurrently with POG 9407 (Cohorts 1 and 2), and the results confirm the prognostic significance of age and MLL rearrangement status. The study had a 4-year EFS and overall survival (OS) of 43.7% and 49.5%, respectively. Age has a very strong effect within the MLL-rearranged group (RHR = 4.42) with a 4-year EFS of 55.7% (standard error (SE) = 8.7) in the older infants (> 90 days) versus an EFS of only 10.6% (SE = 10.0) in the younger group. The CCG-1953 study was designed to test all MLL-rearranged infants (as determined by Southern blot and/or cytogenetics) by RT-PCR for fusion transcripts for t(4;11), t(11;19), and t(9;11). The 5-year EFS for these groups on CCG-1953 therapy (identical to P9407 but without the elimination of decadron, with higher dose methotrexate, longer Maintenance and mandated BMT for MLL-rearranged), was as follows: t(4;11): n = 35, EFS = 29.0% ; t(11;19): n = 20, EFS = 30.0%; t(9;11): n = 9, EFS = 22.2%; and other 11q23: n = 15, EFS = 53.3%.[7]

Based on the above experience, groups identified for risk-directed therapy are listed below. MLL-rearranged infants are all selected for eligibility for FLT3 inhibitor therapy based upon their uniformly high expression of FLT3, and their uniformly inferior EFS compared to that of ALL patients older than 1 year of age. The population proportion and 3-year EFS range from Cohorts 1 + 2 and Cohort 3 are given in parentheses.

Infant Standard Risk (SR): MLL non-rearranged (24% of patients, 3 year EFS 74%-81%)

Infant Intermediate Risk (IR): MLL-rearranged, ≥ 90 days at diagnosis (54% of patients, 3 year EFS 47%-53%)

Infant High Risk (HR): MLL-rearranged, < 90 days at diagnosis (17% of patients, 3 year EFS 5%-7%)

2.3 Rationale for FLT3 Inhibition as a Novel Treatment for MLL-rearranged Infant ALL

2.3.1 FLT3 Background

The FLT3 tyrosine kinase is an important oncogene in adult and pediatric AML, and FLT3 inhibition as a therapeutic strategy is being actively explored. FLT3 has recently been implicated in the pathogenesis of infant and childhood ALL, as well. Gene expression studies have shown that the highest levels of FLT3 mRNA expression occur in cases of infant and childhood ALL with rearrangements of the MLL gene, which account for 80% of infant and 5% of childhood ALL cases.[8,9] The correlation of high FLT3 expression and MLL rearrangement in these studies is very strong. Moreover, several laboratories have demonstrated that leukemic blasts from cases of MLL-rearranged infant ALL also express high levels of

FLT3 at the protein level, and that FLT3 is constitutively phosphorylated in these cases, even in the absence of FLT3 activating mutations, suggesting autocrine activation via coexpression of FLT3 ligand (FL) in these cases.[10-12] In addition, activating mutations of FLT3 (specifically, point mutations in the activation loop of the kinase domain) occur in approximately 15% of infants and children with ALL with MLL gene rearrangements.[9,11,13]

2.3.2 Pre-Clinical Data with FLT3 Inhibitors

The demonstrated importance of FLT3 signaling in the pathogenesis of human leukemia has led to the development of FLT3-targeted agents. Lestaurtinib (CEP-701) is a highly selective small molecule FLT3 tyrosine kinase inhibitor (TKI) with excellent oral bioavailability and an IC_{50} of 3 nM.[14] *In vitro*, lestaurtinib selectively kills primary infant and childhood ALL cells with high-level expression of constitutively activated FLT3, especially those with MLL rearrangements, so that marked lestaurtinib sensitivity was seen in 82% (9 of 11) of MLL-rearranged samples vs. 8% (1 of 13) of samples that lacked MLL rearrangement and expressed low levels of FLT3.[10]

2.3.3 Pre-Clinical Data with Combinations of Chemotherapy and FLT3 Inhibitors

Since monotherapy with any single molecularly targeted agent is unlikely to be curative in acute leukemia, targeted agents are more likely to be effective as components of combination chemotherapy regimens. Lestaurtinib has been shown to result in synergistic killing of MLL-rearranged ALL cells when combined with multiple chemotherapy agents.[15] The degree of synergy is markedly dependent upon sequence of exposure to the agents. Exposure to chemotherapy followed by lestaurtinib results in consistent and strong synergistic cell killing, while simultaneous exposure is in most cases additive. Exposure to lestaurtinib followed by chemotherapy is, in many cases, antagonistic. This sequence dependence is due to the effects of FLT3 inhibition on cell cycle progression. The design of this study takes these important biological findings into account, as lestaurtinib will be given immediately following exposure to standard cytotoxic chemotherapy in an effort to maximize potential synergy, and will not be given for at least 24 hours prior to chemotherapy to avoid potential antagonism.

2.3.4 Clinical Experience with Lestaurtinib

2.3.4.1 Adult Lestaurtinib Phase I

A total of 30 adult patients with advanced solid tumors were enrolled at twice-daily doses of 5 mg (n = 3), 10 mg (n = 3), 20 mg (n = 3), 40 mg (n = 13), 80 mg (n = 7), and 120 mg (n = 1).[16] The majority of patients (67%) received a single 28-day cycle of lestaurtinib. However, 7 patients received study drug for at least 3 months, including 3 patients who were treated for more than 6 months. One patient received 13 cycles of treatment. The most frequently reported adverse events were nausea (63%), diarrhea (47%), anorexia (37%), asthenia (30%), constipation (27%), and vomiting (27%). The incidence of adverse events tended to be greater in patients who received at least 40 mg BID. Most of these events were intermittent, but lasted several days. Dose-limiting toxicities (DLTs) were reported for 1 patient at 80 mg BID (Grade 3 nausea) and 1 patient at 120 mg BID (Grade 3 hypotension). The formal definition of MTD was not met for either of these dosages. Lestaurtinib was rapidly absorbed, with mean t_{max} values ranging from 0.8 to 2.7 hours on Days 1 and 28 across all dosages. At 40 mg BID, the Day 28 mean C_{max} was 3973 ng/mL, and the mean AUC12 was 26630 ng-hr/mL. At 80 mg BID, the Day 28 mean C_{max} was 12117 ng/mL, and the mean AUC12 was 114857 ng-hr/mL. Lestaurtinib did not produce an objective tumor response in any patient. The median duration of treatment was 5 weeks. Three patients had stable disease for more than 6 months and 1 of the patients with small cell lung cancer was stable for almost a year.

2.3.4.2 Adult Lestaurtinib Phase II Single Agent

The activity of lestaurtinib was studied in 18 adults with refractory or relapsed AML with activating mutations of the receptor tyrosine kinase FLT3.[17] The starting dosage of lestaurtinib was raised in this

study from 40 mg BID to 60 mg BID after the first 4 patients showed no response and a cell-based ex-vivo assay of plasma indicated that the inhibition of the FLT3 target may have been suboptimal. Fourteen patients were subsequently enrolled at 60 mg BID, and the dosage for 3 patients was increased to 80 mg BID after approximately 1 month of treatment. The higher doses of 60 and 80 mg BID were well tolerated in this group of patients. At a dosage of 60 mg BID, the ex-vivo assay indicated that a high degree of inhibition (> 90%) of the FLT3 target was maintained over the 12-hour interval between doses. Clinical responses (reduction in peripheral blood or bone marrow blast percentage) were seen in 5 of 14 patients, all of whom had been shown to be refractory to chemotherapy. Serious adverse events of gastrointestinal hemorrhage, fatigue and congestive heart failure in 1 patient each were considered possibly related to lestaurtinib. These events were also considered possibly related to the patients' disease and/or prior treatment.

2.3.4.3 Adult Lestaurtinib Phase II Chemotherapy Combination

An ongoing study randomizes adults with refractory or relapsed FLT3-mutant AML to receive chemotherapy alone or chemotherapy in sequential combination with lestaurtinib (80 mg PO BID).[18] Forty-two patients have been enrolled and 34 have completed the primary endpoint assessment (12 males and 22 females, median age = 58, age range = 26-72). In general, lestaurtinib was well tolerated, with mild to moderate gastrointestinal symptoms and fatigue attributed to the drug. Of the pretreatment leukemia samples available for cytotoxicity analysis, 78% were sensitive to lestaurtinib *in vitro*. Thirteen of 17 (76%) patients achieved a plasma FLT3 inhibitory activity of greater than 85%. All patients who achieved this degree of plasma FLT3 inhibitory activity and whose pretreatment leukemia cells were sensitive *in vitro* to lestaurtinib achieved a clinical response. Conversely, patients with insensitive cells or low drug plasma levels did not respond. Ten of 17 patients randomized to lestaurtinib showed evidence of response (CR or partial response [PR]); while 4 of 17 patients randomized to receive chemotherapy alone had achieved a response. Accrual is ongoing. Lestaurtinib has been well-tolerated in this trial, with mild to moderate gastrointestinal symptoms and fatigue attributed to the drug.

2.3.4.4 Pediatric Lestaurtinib Phase I

A Phase I study of single agent lestaurtinib in children with refractory neuroblastoma (lestaurtinib is also an inhibitor of the Trk family of neurotrophin receptors) is underway. Twenty-two patients (median age = 10.3 yrs, age range = 3.6 - 19.8) have been enrolled (John Maris et al, personal communication). All have been heavily pretreated, with a median of 6 prior regimens (range = 2-11), all 22 patients have received at least 1 autologous bone marrow transplant, and 21 of 22 patients have received radiation therapy. Patients are given lestaurtinib orally twice daily for 5 days, then 2 days off, for 4 weeks (each course is 28 days). Fifty-four courses have been given to the 22 patients (mean age = 2.6, age range = 1-12). No toxicity was seen at doses up to 50 mg/m^2/dose twice daily. Reversible transaminase elevations were seen at 70 mg/m^2/dose twice daily. Accrual continues at 62.5 mg/m^2/dose twice daily. No hematologic toxicity has been seen at any dose level. Trough plasma samples taken from patients on this trial have consistently demonstrated > 90% FLT3 inhibitory activity in ex-vivo plasma bioassays, a level which has been positively correlated with anti-tumor response in the adult AML trials (Patrick Brown, personal communication).[18]

2.4 Hematopoeitic Stem Cell Transplantation (HSCT)

There are single institution reports of outcome of hematopoeitic stem cell rescue (HSCR) in infant ALL showing good outcomes, but they are uncontrolled, have small numbers, and include non-High Risk infants.[19-22] There are also reports of lack of benefit to BMT.[3,23,24] The largest of these reports, concluding that HSCT shows no advantage over chemotherapy, comes from the Ponti de Legno group. This group performed a retrospective comparison of outcomes following treatment with chemotherapy vs. HSCT for 214 infants with t(4;11) ALL treated between 1983 and 1995, which showed a hazard ratio of 1.8 for HSCT compared to chemotherapy.[23,24] This study, while it is a retrospective analysis of 11 groups, does

analyze chemotherapy and HSCT patients in a way that adjusts for "time to transplant", avoiding the bias of reporting HSCT patient survival without comparison to chemotherapy patients.

Approximately 14 (of 74, or 19%) infants registered on POG 9407 and 34 (of 115, or 30%) enrolled on CCG 1953 underwent HSCT. There was no difference in outcome observed for High Risk patients with the MLL gene rearrangement who received conventional chemotherapy (5-year EFS = 48.7% with SE = 10.1%) compared with those who underwent stem cell transplant (5-year EFS = 50.9% with SE = 9.9%; RHR = 1.13). The interfant-99 protocol allowed BMT for High Risk (prednisone-poor responders regardless of MLL) infants. Forty-one infants were transplanted (28 MLL-rearranged, 8 MLL germline, 5 MLL unknown). The DFS was not statistically different for transplants (50%) versus those treated with chemotherapy alone (37%), adjusted for time to transplant (P = 0.19) (R. Pieters, personal communication, submitted).

Based on these data, HSCT in first remission is not a therapeutic option for infants with ALL enrolled on this study.

2.5 Rationale for Chemotherapy

2.5.1 Induction Chemotherapy

AALL0631 Induction chemotherapy was initially based on the COG P9407 (Cohort 3) protocol, which 'passed' specific safety monitoring rules incorporated into that trial after excessive infectious toxicity was encountered during Cohorts 1 and 2, particularly among infants less than 90 days of age. There were 2 changes made to Induction therapy in AALL0631: (1) The daunomycin dose was reduced by 15% (Days 1 and 2) in order to reduce the incidence of mucositis and delay in proceeding to the subsequent phase of therapy; (2) E. coli asparaginase was replaced with pegaspargase.

Four of the first 26 patients enrolled on AALL0631 have died of infections during Induction, and 1 patient has discontinued protocol therapy due to severe non-fatal Induction toxicity.[25] The details of the 5 Induction toxicities on AALL0631 are below (Table 1):

TABLE 1

Age at dx (days)	Type of toxicity	Fatal?	Timing of toxicity
1	Infection (fungal – Aspergillus fumigatus)	Y	Became ill **Day 15**, died Day 23
2	Severe hepatotoxicity/hyperbilirubinemia	N	Bili began rising D**ay 23**, progressed over next 2 weeks
92	Infection (fungal – Candida tropicalis)	Y	First + cx D**ay 17**, progressed over next 2-3 weeks, died Day 33
285	Infection (bacterial – Pseudomonas aeruginosa)	Y	Became ill D**ay 10**, died Day 16
308	Infection (bacterial – Bacillus species)	Y	Became ill D**ay 18**, died Day 19

This prompted a comprehensive review of toxicity for infants with ALL treated on AALL0631, P9407 (Cohort 3 only) and Interfant-99 (a European cooperative group study). The following tables summarize relative Induction death rates for patients in various age groups (based on age in days at diagnosis) on P9407 (Cohort 3), AALL0631 and Interfant-99 (data provided by Rob Pieters).

Age 0 to 6 days

Protocol	N	Deaths	Rate
P9407 c3	2	1	50%
Interfant-99	9	2	22%
AALL0631	2	1	50%

We have concluded that for patients less than one week old at diagnosis, the risk of toxic death is high with all regimens. While numbers are small, the risk appears to be unacceptably high with AALL0631 and P9407 (Cohort 3) protocol therapy, and this risk appears to be less with Interfant-99 protocol therapy.

Age 7 to 29 days

Protocol	N	Deaths	Rate
P9407 c3	3	0	0%
Interfant-99	21	1	5%
AALL0631	0	-	-

We have concluded that for patients from 7 to 29 days of age at diagnosis, we have very little data to assess the risk of toxic death with AALL0631 or P9407 (Cohort 3) protocol therapy, but cannot exclude the possibility that these risks may be excessive. The risk of Induction death appears to be within the expected range with Interfant-99 protocol therapy in this age group.

Age > 30 days

Protocol	N	Deaths	Rate
P9407 c3	137	5	4%
Interfant-99	452	19	4%
AALL0631	24	3	13%

While numbers are small, we are concerned that for patients at least 30 days of age at diagnosis, the risk of toxic death may be excessive with AALL0631 protocol therapy, while the risk of toxic death appears to be lower for both P9407 (Cohort 3) and Interfant-99 in this age group. Notably, the Interfant-99 data are based on a significantly larger number of patients.

In summary: For infants less than 30 days old at diagnosis, it appears that Interfant-99 Induction therapy is associated with lower Induction toxic death rates than either P9407 (Cohort 3) or AALL0631 therapy. For infants greater than 30 days old at diagnosis, it appears that there may be increased risk with AALL0631 Induction therapy compared to P9407 (Cohort 3) or Interfant-99. While P9407 (Cohort 3) passed prospective safety monitoring rules in this population, this is based on a significantly smaller number of patients than the Interfant-99 protocol. Therefore, we have concluded that the most prudent approach will be to adopt the Interfant-99 Induction regimen for all age groups.

It is important to emphasize that long term outcomes for infants with MLL rearrangements are unsatisfactory with either P9407 or Interfant-99 therapy. The primary goal of AALL0631 is to determine if treatment with a modified P9407 chemotherapy backbone with the FLT3 inhibitor (lestaurtinib) improves outcome for these infants. With this is mind, we believe that it is critical to have an Induction regimen that is safe and well tolerated, thereby allowing us to evaluate the potential efficacy of lestaurtinib, which is the primary objective of the AALL0631 trial.

An important consideration is whether we will be sacrificing efficacy by adopting the Interfant-99 Induction regimen. The available data are encouraging in this regard. For patients less than 30 days old, the Induction complete remission (CR) rate was 87% (26 of 30, with 2 failures due to toxic deaths) on Interfant-99, which was not significantly different than the CR rate of 93% (394/424) for older patients on Interfant-99, or the CR rate of 90% (97/108) for all patients on P9407 Cohort 3 (where remission status was determined at the end of the Induction Intensification course at Week 8).

The following table shows a direct comparison of the Induction therapy given on these protocols. A key part of the Interfant-99 Induction regimen that will be new to COG trials is a 7-day prednisone prophase.

	Interfant		AALL0631/P9407 c3		Comparison
Drug	**Details**	**Cum**	**Details**	**Cum**	
PRED/ DEX	PRED 45 mg/m^2 Days 1-7, DEX 4.5 mg/m^2 Days 8-28, taper Days 29-35	PRED 315 mg/m^2, DEX 94.5 mg/m^2 (plus taper)	PRED 40 mg/m^2 Days 1-21	PRED 840 mg/m^2	similar
VCR	1.125 mg/m^2 Days 8,15,22,29	4.5 mg/m^2	0.05 mg/kg Day 1, 15, 0.03 mg/kg Day 8	0.13 mg/kg (~4 mg/m^2)	similar
DAUN	22.5 mg/m^2 Days 8,9	45 mg/m^2	2.6 mg/kg Days 1,2 (9407: 3 mg/kg)	5.2 mg/kg (~150 mg/m^2) (9407: 6 mg/kg, ~180 mg/m^2)	0631 >> interfant
PEG-ASP	E.coli L-ASP 7500 IU/m^2 (Elspar) IV or IM Days 15,18,22,25,29,33	45,000 IU/m^2	0631: PEG-ASP 2500 IU/m^2 IM Day 4 9407: E.coli L-ASP 6000 IU/m^2 IM x 8 (Days 4,6,8,10,12,15,17,19)	0631: PEG-ASP 2500 IU/m^2 9407: E.coli L-ASP 48,000 IU/m^2	similar
ARAC	56.25/m^2 Days 8-21	787.5/m^2	-	-	interfant >> 0631
CPM	-	-	250 mg/m^2 q12 x 4 Days 3, 4	1000 mg/m^2	0631 >> interfant
IT	MTX (6 mg) Day 1, ARAC (15 mg) + HC (12 mg) Day 15, MTX + HC Day 29	MTX 12 mg, ARAC 15 mg, HC 24 mg	ITT Days 1, 8, 15	MTX 22.5 mg, ARAC 45 mg, HC 22.5 mg	0631 >> interfant

NOTES:

1. For Interfant, non-IT drugs dose reduced 11% for patients < 6 months old at diagnosis.
2. For AALL0631, dauno dose reduced to 2.1 mg/kg for 6-9 months old at diagnosis, and to 1.7 mg/kg for < 6 months old at diagnosis.

Based on these data, we are adopting the Interfant-99 Induction regimen for all patients, with the following modifications:

1. The steroid taper that is included in the Interfant-99 Induction regimen will be eliminated.
2. E. coli asparaginase (ASP; Elspar) will be given IM (not IV or IM, as in Interfant-99) if available. If unavailable, Erwinia is to be substituted as per Section 5.1.
3. For patients less than 7 days old at diagnosis, an additional 25% dose reduction will be applied to all non-intrathecal chemotherapy.

The table below summarizes the amended Induction regimen:

Amended AALL0631		
Drug	**Details**	**Cumulative**
PRED/DEX	PRED 45 mg/m^2 Days 1-7, DEX 4.5 mg/m^2 Days 8-28	PRED 315 mg/m^2, DEX 94.5 mg/m^2
VCR	1.125 mg/m^2 Days 8,15,22,29	4.5 mg/m^2
DAUN	22.5 mg/m^2 Days 8,9	45 mg/m^2
E.coli L-ASP	7500 IU/m^2 IM Days 15,18,22,25,29,33	45,000 IU/m^2
ARAC	56.25 mg/m^2 Days 8-21	787.5 mg/m^2
CPM	-	-
IT	MTX (6 mg) Day 1 ARAC (15 mg) + HC (12 mg) Day 15, MTX + HC Day 29	MTX 12 mg, ARAC 15 mg, HC 24 mg

NOTES:
1. Non-IT drugs dose reduced 11% for patients < 6 months old at diagnosis.
2. Non-IT drugs dose reduced an additional 25% for patients < 7 days old at diagnosis.

Following this change, induction mortality was significantly lower for patients in Cohort 2 (modified Induction) versus Cohort 1 (original Induction), 2/67 (3%) vs. 4/26 (15.4%), p=0.049.[26] All deaths during Induction were infection related except one from progressive disease (Cohort 2). Sterile site infections were also more common in Cohort 1 (Table 1). There were no clinically significant Grade 3-4 non-infectious toxicity differences between Cohorts 1 and 2.

2.5.2 Post-Induction Chemotherapy Backbone for MLL-R Patients

The post-Induction chemotherapy to be given to all patients in this study will continue to be based upon the post-Induction chemotherapy regimen given on P9407, Cohort 3.

Several modifications have been made to post-Induction chemotherapy with the goal of improving outcome by reducing relapse risk without significantly increasing regimen-related toxicity.

- Replace E coli asparaginase with pegaspargase in Re-Induction, Consolidation and Continuation I

  Currently the asparaginase of choice in all COG ALL protocols is pegaspargase, due to reduced toxicity and ease of delivery. We will incorporate this change into this protocol for uniformity among ALL protocols, and will monitor for unexpected toxicities.

- Change post-Induction steroids from prednisone to dexamethasone

  No dexamethasone-related deaths were observed during Re-Induction for Cohorts 1 and 2 of P9407, and minimal toxicity has been observed during Re-Induction for Cohort 3 of P9407. Dexamethasone is likely to enhance disease (marrow and CNS) control.

- Intensify Continuation with modifications of VP/CTX pulses

  P9407 Continuation included 2 5-day pulses of VP/CTX. As of March 2006, there have been 23 relapses for Cohort 3. Thirteen (57%) of these (7 BM, 4 CNS and 2 testicular) have occurred between Week 18 (beginning of Continuation) and Week 48 (end of therapy evaluation), with 3 of these being noted with the end of therapy marrow/LP (1 CNS relapse, 2 BM relapses). This is a greater relapse rate than was noted for Cohorts 1 and 2 (only 2 of 13 relapses occurred during therapy). Therefore, intensifying the existing VP/CTX pulses is likely to enhance disease control during this less intensive

phase of therapy, while also providing additional HDAC exposure which is desirable, given *in vitro* data suggesting that infant ALL cells are more sensitive to Ara-C than ALL cells from older children.[27,28] Intensive pulses will be modified such that VP/CTX will be followed by 1 week of HDAC/PEG-ASP. While the potential for enhanced toxicity during Continuation I is increased, there is likely to be a significant advantage to intensifying therapy at this point.

- Change weekly MTX in Continuation from 20 mg/m^2 intramuscular (IM) to 20 mg/m^2 intravenous (IV)

  Methotrexate is changed from IM to IV administration for patient comfort and uniformity among ALL protocols.

- Extend Continuation, resulting in 24 months of total therapy

  Concern has been raised that the Continuation in P9407 (total 46 weeks of therapy) is of insufficient duration. There have been 3 relapses noted at "off-protocol therapy" marrow in Cohort 3 of P9407. In addition, there have been an additional 5 relapses within 5 months of stopping therapy. Extended Continuation may enhance disease control with minimal risk of increased toxicity.

2.5.3 Post-Induction Chemotherapy Backbone for MLL-G Patients

Given the small number of MLL-G infants that will enroll in this trial, we do not anticipate being able to ask and answer a rigorous efficacy question. We propose to treat these patients with an Interfant-99 based Induction chemotherapy regimen identical to that given to the MLL-R infants. MLL-G infants receive a post-Induction chemotherapy regimen identical to Cohort 3 of P9407 until Week 42, except for 3 modifications: (1) change post-Induction steroid to dexamethasone, (2) replace E coli asparaginase with pegaspargase in Re-Induction and Consolidation, and (3) change weekly MTX in Continuation from IM to IV. After Week 42, MLL-G patients will begin an extended Continuation period similar to Maintenance therapy that is given in standard ALL protocols, for a total duration of therapy of 2 years. This change is being made both to address the risk of late relapse that has been seen for MLL-G patients enrolled in prior studies.

2.6 Rationale for Study Design

2.6.1 Overview

Lestaurtinib has never been tested in infants, and so this study will be conducted in two phases: a safety/activity phase, with the objective of determining a safe, tolerable and biologically active dose of lestaurtinib given in sequential combination with chemotherapy in MLL-R infants, and an efficacy phase, with the objective of estimating the 3-year EFS of infants with MLL-R ALL treated with chemotherapy plus the FLT3 inhibitor lestaurtinib.

2.6.2 Rationale for Design of Safety/Activity Phase

During the safety/activity phase, MLL-R infants enrolled at the institutions listed on the AALL0631 protocol website (COG Phase I/Pilot Consortium plus a number of additional institutions) will receive chemotherapy plus lestaurtinib. MLL-R infants enrolled at other institutions during this phase will be treated with chemotherapy only. MLL-R infants treated with lestaurtinib during the safety/activity phase will be stratified into IR (≥ 90 days of age at diagnosis) and HR (< 90 days of age at diagnosis) arms to facilitate independent toxicity assessments and dose adjustments, which will allow for potentially different pharmacokinetic and toxicity profiles of older and younger infants. Decisions regarding dose adjustments based on toxicity and biologic activity will be made according to the algorithm in Section 4.2.1. The presence or absence of a DLT attributable to lestaurtinib will be determined for each patient after the first 2 courses of lestaurtinib (i.e., during the Induction Intensification and Re-Induction

phases), which will facilitate timely assessment of safety and need for dose adjustment. The definition of DLTs attributable to lestaurtinib to be used in this study is detailed in Section 4.2.3.

2.6.3 Rationale for Starting Dose of Lestaurtinib

Age group	Wt (kg)	BSA (m^2)	Dose (mg/m^2/day)	Dose (mg/kg/day)	Dose (mg/day)	Volume of dose of 5 mg/mL mixture (mL/dose)
Neonate	3.2	0.2	56	**3.5**	11	1.1
6 wk old	4.6	0.27	60	**3.5**	16	1.6
3 mo old (89 days)	6	0.32	66	**3.5**	21	2.1
3 mo old (90 days)	6	0.32	75	**4**	24	2.4
6 mo old	7.8	0.38	82	**4**	31	3.1
9 mo old	9.1	0.43	85	**4**	36	3.6
12 mo old	10.1	0.46	88	**4**	40	4
9 yr old (Nb patient)	28.5	1.03	**125**	4.5	129	N/A
Adult (AML trials)	70	1.73	92.5	2.3	**160**	N/A

The starting dose of lestaurtinib on this study will be 3.5 mg/kg/day divided BID for < 90 days of age, and 4 mg/kg/day divided BID for > 90 days of age. Due to the lack of clinical experience with lestaurtinib in infants (who have proven to be unpredictable in terms of pharmacokinetics and pharmacodynamics), dosing on a per kg basis seems the most appropriate initial strategy. The dose tolerated in older children in the lestaurtinib single agent Phase I neuroblastoma trial was 125 mg/m^2/day divided BID, and the dose tolerated in adults in the combination lestaurtinib and chemotherapy Phase II AML trial was 160 mg/day divided BID. The table above shows a comparison of these doses with the proposed starting doses in this trial for infants of various weights and BSA (based on average for males at listed age). Compared to the Phase I pediatric dose, which is a more relevant dose comparison group for this trial than the adult group, our proposed starting doses are 11%-23% lower on a per kg basis, and 30%-55% lower on a per m^2 basis. Compared to the adult dose, the starting doses on this trial are 5%-39% lower on a per m^2 basis and 52%-74% higher on a per kg basis (which is less relevant than m^2 when comparing adult and pediatric dosing).

2.6.4 Rationale for Design of Efficacy Phase

This study initially used a randomized design (prior to Amendment #5) to evaluate whether the addition of lestaurtinib to a modified P9407 chemotherapy backbone results in improved outcome for MLL-R infant ALL. A randomized design allows for a direct comparison of the 2 arms, minimizing confounders unrelated to lestaurtinib (such as improvements in supportive care). In addition, it allows for several modifications to the P9407 chemotherapy backbone which may improve overall outcome. The specific modifications, and the rationale for each, are detailed in Section 2.5.

As of the activation of Amendment #5, the design of the efficacy phase is changed to accommodate the lack of drug availability for the duration of the planned randomized study. MLL-R patients will be non-randomly assigned to receive lestaurtinib at the dose proven to be safe and achieve biologically active levels in the safety phase. In addition, the duration of lestaurtinib treatment will be reduced such that patients will discontinue lestaurtinib after Continuation I (Week 45), which will be 1 year from diagnosis.

2.6.5 Successful Completion of Safety/Activity Phase

2.6.5.1 IR patients

Ten evaluable IR patients received lestaurtinib, 5 patients each at dose levels (DL) 1 (4 mg/kg/day) and DL2 (5 mg/kg/day). There were no DLTs at either dose level during the first 2 courses of lestaurtinib. Results from the plasma inhibitory assay (PIA) were used to assess the biologic activity of lestaurtinib. There were a total of 5 trough time points for each patient: Days 24 and 27 of Induction Intensification;

Days 9, 12, and 19 of Re-Induction. For the 5 IR patients treated at DL2, 4 out of 5 had adequate FLT3 inhibitory plasma levels for the majority of the 5 trough samples: 1 patient had adequate levels at 1 time point, 2 patients had adequate levels at 3 time points, and 2 patients had adequate levels at 5 time points. Thus DL2 (5 mg/kg/day divided BID) was identified as a tolerable and biologically active dose for IR patients, and the efficacy phase began for IR patients on 01/28/11.[29]

2.6.5.2 HR patients

Ten evaluable HR patients received lestaurtinib, 5 patients each at dose levels (DL) 1 (3.5 mg/kg/day) and 2 (4.25 mg/kg/day). There were no DLTs at DL1 and 1 DLT at DL2 during the first 2 courses of lestaurtinib. The DLT was Grade 4 intestinal perforation secondary to severe typhlitis during neutropenia following re-Induction, possibly related to lestaurtinib. The patient was taken off protocol due to inability to tolerate further chemotherapy and died of progressive disease. Results from the plasma inhibitory assay (PIA) were used to assess the biologic activity of lestaurtinib. There were a total of 5 trough time points for each patient: Days 24 and 27 of Induction Intensification; Days 9, 12, and 19 of re-Induction. For the 5 HR patients treated at DL2, 4 out of 5 had adequate FLT3 inhibitory plasma levels for the majority of the 5 trough samples: 1 patient did not have adequate levels at any time point, 1 patient had adequate levels at 3 time points, 2 patients had adequate levels at 4 time points and 1 patient had adequate levels at 5 time points. Thus DL2 (4.25 mg/kg/day divided BID) was identified as a tolerable and biologically active dose for HR patients, and the efficacy phase began for HR patients on 02/03/12.[30]

2.7 Rationale for Correlative Studies

2.7.1 Assessing Biologic Activity of Lestaurtinib Using FLT3 Plasma Inhibitory Activity (PIA) Assay

The advent of molecularly targeted agents has created a need for new early phase trial designs that are based primarily on determining the dose necessary to achieve the desired biologic activity, rather than the MTD. In practice, directly assessing whether a targeted agent is consistently "hitting the target" in the context of a clinical trial is challenging, requiring not only multiple invasive procedures to obtain sufficient numbers of tumor cells for evaluation, but also the availability of a validated, technically feasible, real-time assay of functional target inhibition. The few cases where this type of assessment has been attempted have been leukemia clinical trials where persistently high peripheral leukemic blast counts despite exposure to the investigational drug have allowed collection of tumor cells at multiple time points with simple blood draws. Even in these rare (and unenviable) situations, such assessments have been largely unsuccessful for a variety of reasons. In the trial described here, patients will have already been exposed to 54 days of intensive Induction chemotherapy prior to the onset of lestaurtinib therapy on Day 55. In the vast majority of these cases, there will be inadequate numbers of circulating leukemic cells on Day 55 to allow direct assessment of FLT3 inhibition by collecting peripheral blood, and it would be neither feasible nor ethically acceptable to perform bone marrow aspiration on patients at the multiple time points necessary for adequate evaluation of consistent FLT3 inhibition in tumor cells. Standard pharmacokinetic assays accurately measure the concentration of total drug in plasma, but do not measure the amount of free drug, which varies widely depending upon the affinity of a drug for the various plasma proteins (e.g., albumin, alpha-1-acid glycoprotein (AGP) and the concentration of these proteins in an individual patient's plasma. Since only the free, unbound fraction of lestaurtinib is available to inhibit FLT3 in target cells, and since lestaurtinib is known to be greater than 99% bound to plasma proteins, pharmacokinetic values cannot be used as a valid surrogate for lestaurtinib biologic activity. While direct measurement of free lestaurtinib levels in patient plasma would be expected to correlate nicely with the degree of FLT3 inhibition achieved in target leukemic cells, reliable assays of free lestaurtinib levels are not available.

In light of these limitations, we have developed an assay which can act as a powerful surrogate for *in vivo* FLT3 inhibition in patients receiving lestaurtinib by measuring FLT3 plasma inhibitory activity (PIA).[31]

The results of the PIA assay will be used to assess the biologic activity of lestaurtinib in this novel clinical trial design.

2.7.2 Correlating Clinical Responses with PIA and *In Vitro* Lestaurtinib Sensitivity

In order for a leukemia patient to have a favorable response to a molecularly targeted therapeutic agent, 2 requirements must be met: (1) the leukemia cells must be dependent, at least in part, upon the activity of the molecular target for its survival; and (2) sufficient levels of the agent must be delivered to the leukemia cells to inhibit the target. Using the MTT cytotoxicity and annexin V binding apoptosis assays, we have demonstrated that in over 80% of cases, leukemic cells isolated from patients with MLL-R ALL are dependent on activated FLT3 signaling for their survival, since when FLT3 is selectively inhibited by exposure to lestaurtinib, the cells undergo apoptosis and die (and are therefore considered "sensitive" to lestaurtinib). The degree of inhibition of FLT3 activity required to achieve this cytotoxicity is approximately 90% relative to untreated control, and this degree of inhibition must be sustained over at least 48 hours. A minority of MLL-R samples demonstrate *in vitro* resistance to FLT3 inhibition, a phenomenon that will be explored in detail in correlative studies introduced in Section 2.7.3. We have also developed an assay that is able to reliably measure the FLT3 inhibitory activity in patient plasma (plasma inhibitory activity, or PIA) while receiving lestaurtinib. The major significance of this assay is that it has proven to be a reliable surrogate for the degree of FLT3 inhibition achieved in the patient's leukemia cells, which is often not amenable to direct assessment. Thus, with the availability of *in vitro* assays of lestaurtinib sensitivity and the *ex vivo* PIA assay, we will be able to test whether the 2 requirements for a favorable response are met for each patient. We hypothesize that consistently achieving ≥ 90% FLT3 PIA at trough time points in a patient whose diagnostic blasts are lestaurtinib-sensitive *in vitro* will be predictive of clinical response, and that a lack of *in vitro* sensitivity **or** a failure to consistently achieve these levels of inhibition will be predictive of treatment failure. If the model proves to be predictive, we may be able to use it in future trials to select appropriate patients for treatment with lestaurtinib, and to individualize dosing to ensure that each patient has a chance to derive maximal benefit from the therapy.

2.7.3 Determining Mechanisms of Resistance to Lestaurtinib

Approximately 15% of MLL-R samples obtained at the time of diagnosis are resistant to the *in vitro* cytotoxic effects of lestaurtinib. There has been good correlation between *in vitro* resistance and clinical resistance in adults treated thus far on the ongoing Phase II trial of chemotherapy plus lestaurtinib in adults with relapsed and refractory FLT3-mutant AML. In a limited number of these resistant samples, we have seen persistent phosphorylation/activation of one or more of the signaling proteins known to be downstream of FLT3 (such as STAT5, MAP kinase, or AKT) despite inhibition of FLT3 phosphorylation, suggesting that the underlying basis of lestaurtinib resistance in some cases may be mutations in one or more signal transduction proteins other than FLT3. The correlative studies proposed here will more fully explore the phenomenon of inherent resistance to FLT3-inihibtor induced cytotoxicity. Acquired resistance during therapy is another potential problem. Acquired resistance to imatinib in chronic myelogenous leukemia (CML) patients is most often due to emergence of CML clones with point mutations that disrupt binding of imatinib to BCR-ABL, resulting in reactivation of BCR-ABL kinase activity in these cells. Recognition of this fact has led to the development of a second generation of BCR-ABL inhibitors that are active against the known resistance-inducing mutations. This experience suggests that acquired resistance-inducing mutations in FLT3 or one of its downstream signaling proteins are likely to be present in samples obtained from patients with progressive or relapsed disease on lestaurtinib therapy, particularly in those whose pre-therapy samples demonstrate *in vitro* sensitivity. Other potential mechanisms of acquired resistance include factors independent of the leukemic cells, such as an increase in the clearance of lestaurtinib (due to upregulation of metabolizing pathways, for example) or a decrease in free drug levels due to increases in plasma protein binding. The correlative studies in this trial will investigate these potential molecular bases of acquired resistance in patients that relapse or progress during or after lestaurtinib therapy. Successfully identifying one or more of these inherent or acquired

resistance mechanisms may potentially allow for selection of patients most likely to respond to lestaurtinib, and could lead to novel therapies able to overcome resistance.

2.7.4 Minimal Residual Disease

While no studies have yet been completed using MRD in infant ALL, all studies in childhood ALL using MRD techniques have shown significant correlations between end-Induction tumor burden and outcome.[31-37] Incorporation of MRD assessments into this study will provide additional data and understanding of the role of MRD in predicting disease recurrence and response to therapeutic interventions in infant ALL. As novel agents become available, MRD analysis may lay the groundwork for evaluation of new agents in infant ALL when added to this therapeutic backbone. Studies in childhood ALL show that patients can be divided into 3 groups: 1) no end-Induction MRD detected (42% to 75% of the total); 2) intermediate levels of MRD (10^{-3} – 10^{-2}, 42% to 20%); 3) and MRD high levels (> 10^{-2}, 5% to 16%). Patients without evidence of MRD have an excellent outcome (3-year EFS > 90%) whereas those with high levels have an exceedingly high relapse rate (3-year EFS = 26%-28%).

Over the past decade, a number of strategies have been developed to monitor MRD in ALL.[38-40] Flow-cytometric detection of residual blast cells has a sensitivity of 10^{-3} to 10^{-4} and relies on 3 and 4 color antigen detection of 1 (or preferably 2) surface phenotypes unique to leukemia and not present on normal cells. This technique can be applied to 98% of all newly-diagnosed children with ALL.[32,33,41,42] Drs. Brown and Murphy at Johns Hopkins have developed a sensitive and reliable multiplex quantitative RT-PCR assay to detect the 3 most common MLL gene rearrangements in infant ALL (MLL-AF4, MLL-ENL and MLL-AF9), adapted from a published technique.[43]

Flow MRD data were collected prospectively on P9407 (measured at Week 8, Week 18 and end therapy). Molecular MRD data are being generated retrospectively at these same timepoints for patients with banked specimens. Comparisons will be made between the Week 10, Week 20/21 and off therapy MRD between the current study and P9407 to determine whether the changes in therapy are associated with changes in MRD patterns at the various timepoints. We will also determine whether MRD by either methodology at any timepoint is predictive of outcome. This analysis will be performed on patients from the 2 studies individually, and with patients from the 2 studies combined for the shared timepoints. The Week 6 MRD determination has been added in this population specifically to: (1) compare the impact of end Induction MRD between infants and older children with ALL, and (2) characterize the impact of the addition of lestaurtinib to MRD patterns between Arm B and Arm C [Week 6 MRD is pre-lestaurtinib, Weeks 10 and 20 MRD are after the lestaurtinib doses in Induction Intensification (Week 10 MRD), and Re-Induction/Consolidation (Week 20 MRD)].

2.7.5 Gene Expression Profiling

The gene expression profiling studies associated with this protocol are based on 2 hypotheses: (1) that we can identify gene expression profiles and develop classifiers predictive of *in vitro* sensitivity or resistance of infant ALL samples to the FLT3 inhibitor lestaurtinib; and (2) that we can extend and validate a novel molecular classification scheme we have developed for infant leukemia in this prospective cohort of infant leukemia patients. Using Affymetrix oligonucleotide microarrays, Dr. Cheryl Willman's laboratory obtained expression profiles from an initial retrospective cohort of 126 infants with acute leukemia (78 ALL, 48 AML). Using unsupervised learning algorithms and novel data visualization tools (VxInsight and Principal Component Analysis (PCA)), they discovered 3 novel, statistically robust clusters of infant leukemia that did not correlate with traditional morphologic (AML vs. ALL) or cytogenetic (presence or absence of MLL rearrangements) parameters (Cheryl Willman, personal communication). We now propose to determine if this molecular classification scheme is reproducible by validating it in a new prospective cohort of infant patients registered to COG leukemia trials using newer high density Affymetrix HG_U133 Plus2.0 Arrays, including the infant leukemia cases registered to this trial.

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration via Remote Data Entry (RDE)

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

3.1.2 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206), emailed (CTSURegulatory@ctsu.coccg.org), or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

3.1.3 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

3.1.4 Timing

PATIENTS MUST BE ENROLLED ON A COG ALL CLASSIFICATION STUDY (AALL08B1) BEFORE TREATMENT ON AALL0631 BEGINS. PATIENTS THAT BEGIN PROTOCOL THERAPY FOR LEUKEMIA, PRIOR TO ENROLLMENT ON THE CLASSIFICATION STUDY, ARE INELIGIBLE FOR BOTH THE CLASSIFICATION AND COG ALL THERAPEUTIC TRIALS. The AALL08B1 Institutional Pre-Induction Data Form should be completed within 72 hours of enrolling on this study. If the data is not completed in a timely fashion, the patient will be made inevaluable for the classification and therapeutic trials. Study enrollment must take place within five (5) calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than ***five (5)*** calendar days after enrollment.

Systemic chemotherapy must start within 72 hours of initial intrathecal (IT) therapy specified in Section 4.4.

3.1.5 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.1.6 Treatment Assignment (Callback)

The Callback CRF must be submitted for all patients in order to obtain a post-Induction treatment assignment. Note: In order to complete this CRF, the MLL gene rearrangement status must have been previously entered into eRDE. The Callback CRF should be submitted when the patient's counts have recovered and he/she is ready to proceed to Induction Intensification (Day 1 Week 6 of therapy). All patients with MLL-G (SR) will be assigned to Arm A; all patients (in the US and Canada, see Section 3.1.7 below) with MLL-R (IR and HR) will be assigned to Arm C. **Week 6 therapy must begin within 5 days of treatment assignment.**

3.1.7 Institutional Participation

This study is open to COG member sites in the US and Canada for the lestaurtinib efficacy phase. Patients from sites outside the US and Canada can enroll on the study but if they are found to be MLL-R are not eligible to continue on study post-Induction (lestaurtinib is not available for distribution outside of the US and Canada).

3.2 Patient Criteria

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). 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 which will serve as the source document for verification at the time of audit.**

3.2.1 Classification Study

Patients must be enrolled on a COG ALL Classification Study (AALL08B1) prior to enrollment on AALL0631.

3.2.2 Age

Patients must be < 366 days of age at the time of diagnosis; for neonates in the first month of life, patients must be > 36 weeks gestational age at the time of diagnosis.

3.2.3 Diagnosis

3.2.3.1

Patients must be newly diagnosed with acute lymphoblastic leukemia (ALL) or acute undifferentiated leukemia (AUL). Patients with T-cell ALL are eligible. Patients with bilineage or biphenotypic acute leukemia are eligible, provided the morphology and immunophenotype are predominately lymphoid.

3.2.3.2

Patients with mature B-cell ALL or acute myelogenous leukemia (AML) are NOT eligible.

3.2.3.3

Patients with Down syndrome are NOT eligible.

3.2.4 Prior Therapy

Patients must be previously untreated with the exception of steroids and intrathecal chemotherapy. No other systemic chemotherapy may have been administered. Patients receiving prior steroid therapy are eligible for study. Any amount of steroid pretreatment will not affect initial Induction assignment as long as the patient meets all other eligibility criteria. IT chemotherapy **per protocol** is allowed for patient convenience at the time of the diagnostic bone marrow or venous line placement to avoid second lumbar puncture. (Note: the CNS status must be determined based on a sample obtained prior to administration of any systemic or intrathecal chemotherapy, except for steroid pretreatment as discussed in Section 4.1.1.) Systemic chemotherapy must begin within 72 hours of this IT therapy.

3.2.5 Regulatory

3.2.5.1

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

3.2.5.2

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

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 per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview

All patients will be treated with a common 5-week Induction course after enrollment, as detailed in Section 4.4. Based on age at diagnosis and MLL gene rearrangement status, patients will be stratified into risk groups as follows:

Standard Risk (SR): MLL-G (germline, or non-rearranged)

Intermediate Risk (IR): MLL-R (rearranged), age ≥ 90 days at diagnosis

High Risk (HR): MLL-R, age < 90 days at diagnosis

SR patients will be non-randomly assigned to receive chemotherapy alone as detailed in Section 4.5. There will be some patients for whom MLL status is indeterminate. These patients are to be taken off study.

During the initial safety/activity phase, IR and HR patients who enroll at institutions other than those listed on the AALL0631 protocol website (COG Phase I/Pilot Consortium plus additional institutions) or who enroll during periods where lestaurtinib is unavailable due to toxicity evaluations, will receive chemotherapy alone as detailed in Section 4.6. Please note that IR/HR patient transfers to an institution listed on the AALL0631 protocol website are allowed, if the patient's family wishes to receive lestaurtinib. IR and HR patients who enroll at one of the institutions listed on the AALL0631 protocol website will be assigned to receive a combination of chemotherapy and lestaurtinib as detailed in Section 4.7, with the dose of lestaurtinib determined according to Section 4.2. The safety/activity phase will be done separately and independently for IR and HR patients.

When the safety/activity phase identifies a dose of lestaurtinib that is safe, tolerable and biologically active for the IR and HR arms, then the study will proceed to an efficacy phase for that arm. During the efficacy phase, IR and HR patients enrolled at institutions in the US and Canada will non-randomly be assigned to receive a combination of chemotherapy and lestaurtinib (at the dose identified in the safety/activity phase) as detailed in Section 4.7.

Note: as of 01/28/11 the safety/activity phase for Intermediate Risk patients was completed, and the randomized efficacy phase began at DL2 (5 mg/kg/day).

Note: as of 02/03/12, the safety/activity phase for High Risk patients was completed, and the randomized efficacy phase began at DL2 (4.25 mg/kg/day).

4.1.1 Definitions

INITIAL WBC:
The first WBC at the treating COG institution. If prior therapy (i.e., steroids) has been administered, then the initial WBC prior to therapy should be used.

INITIAL PLATELET COUNT:
The first platelet count at the treating COG institution or the count before transfusion of platelets if transfused prior to arrival.

INITIAL HEMOGLOBIN:
The first hemoglobin at the treating COG institution, or the hemoglobin prior to intravenous fluid or red cell transfusions, whichever occurred first.

STEROID PRETREATMENT:
Patients who have received any amount of oral or IV steroids prior to study entry will be eligible for enrollment, provided patient meets all other eligibility requirements. The "presteroid" age of the patient will be used to determine risk classification (IR vs. HR) for MLL-R patients. Inhalational steroids are not considered as pretreatment.

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

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

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

METHOD OF EVALUATING INITIAL TRAUMATIC LUMBAR PUNCTURES (Steinherz/Bleyer algorithm):
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 algorithm should be used to distinguish between CNS2 and CNS3 disease:

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

A patient with CSF WBC ≥ 5/µL, CSF RBC ≥ 10/µL, and cytospin positive for blasts, whose CSF WBC/RBC ratio is at least 2 X greater than the blood WBC/RBC ratio, has CNS3b disease at diagnosis. Otherwise, the patient has CNS2c disease.

Example: CSF WBC = 60/µL; CSF RBC = 1500/µL; blood WBC = 46000/µL; blood RBC = 3.0 X 10^6/µL:

$$\frac{60}{1500} = 0.04 > 2 \times \frac{46000}{3.0 \times 10^6} = 0.015$$ (patient has CNS3b disease)

TESTICULAR LEUKEMIA AT DIAGNOSIS:
Unilateral or bilateral testiculomegaly. Biopsy is required if clinical findings are equivocal or suggestive of hydrocele or a non-leukemic mass.

BONE MARROW STATUS:
M1: < 5% lymphoblasts
M2: 5 - 25% lymphoblasts
M3: > 25% lymphoblasts.

RELAPSE: Any recurrence of disease whether in marrow or extramedullary site. Relapse should be histopathologically confirmed.

CNS Relapse: Positive cytomorphology and > 5 WBC/µL OR positive cytomorphology with CSF WBC 0-4/µL on two successive occasions one month apart. If any CSF evaluation shows positive cytomorphology and < 5 WBC/µL, a second CSF evaluation is required in greater or equal to 4 weeks. Identification of leukemic clone in CSF by flow cytometry (TdT, CD19, CD10, etc) or FISH for diagnostic karyotypic abnormality is encouraged.

Testicular Relapse: Must be documented by testicular biopsy, in the absence of concomitant bone marrow relapse.

Bone Marrow Relapse: Patients with an M3 marrow at any point after the beginning of Re-Induction (Week 10).

4.1.2 Concomitant Medications Restrictions

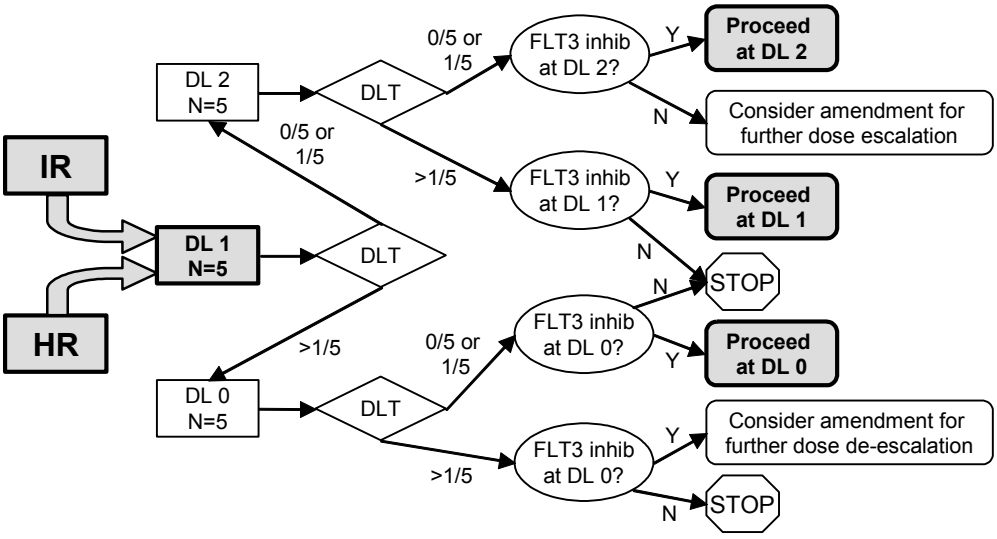
4.1.2.1
Patients cannot receive any non-protocol chemotherapy or investigational therapy while on this study.

4.1.2.2 CYP3A4/5 Inhibitors:
Lestaurtinib is metabolized by the cytochrome P450 isoform CYP3A4/5. Potent inhibitors of CYP3A4/5 are likely to inhibit lestaurtinib metabolism and increase systemic exposure. Therefore, concomitant treatment with lestaurtinib and the following medications should be avoided: azole antifungals (e.g., fluconazole and voriconazole), cyclosporine, erythromycin, clarithromycin, troleandomycin, HIV (human immunodeficiency virus) protease inhibitors, and nefazodone (see Appendices I and II for additional details).

4.1.2.3 CYP3A4/5 Inducers:
It is also likely that inducers of CYP3A4/5, such as carbamazapine, dexamethasone, rifampin, phenobarbital, phenytoin and St. John's Wort will reduce the plasma exposure to lestaurtinib. Concomitant administration of these drugs is also discouraged, except for dexamethasone as prescribed in the treatment regimen (see Appendix II for additional details).

4.2 Safety/Activity Phase (Completed)

4.2.1 Schematic



	< 90 days old (mg/kg/day divided BID)	≥ 90 days old (mg/kg/day divided BID)
DL 0	2.75	3
DL 1	3.5	4
DL 2	4.25	5

4.2.2 Definition of Dose-Limiting Toxicity (DLT)

Defining DLT of a novel agent added to a backbone of intensive chemotherapy is challenging, due to the high baseline toxicity rate associated with the chemotherapy alone. This is particularly true for infants, who have been especially vulnerable to chemotherapy-related toxicities. The major toxicity noted with the chemotherapy backbone (P9407 Cohort 3) was infectious toxicity associated with chemotherapy-induced myelosuppression. Grade 3 or greater infectious toxicity was reported in the majority of patients, and Grade 3 or greater myelosuppression was universal, during Phase I (defined as Weeks 1-7 of therapy, including Induction and Induction Intensification blocks), but both were significantly less common after Phase I. Most of the post-Phase I serious infectious toxicities and myelosuppression were associated with high dose cytarabine in Consolidation. Brief (< 2 weeks) delays in the scheduled start of subsequent chemotherapy courses due to delayed neutrophil and/or platelet recovery was common, but it was rare for chemotherapy-induced myelosuppression to cause delays of 3 weeks of greater. Non-hematologic and non-infectious toxicities that were severe (≥ Grade 3) and occurred with a frequency of ≥ 10% included: stomatitis (24% for all phases of therapy, mostly in Phase I), diarrhea (17% for all phases, mostly in Phase I), AST/ALT elevation (17% for all phases, about half in Phase I) and neurologic toxicities (10%, about one-third in Phase I), which were primarily seizures related to intrathecal or high dose methotrexate and peripheral neuropathy related to vincristine. In addition to these "serious and unexpected" toxicities, other toxicities are expected in infants undergoing intensive chemotherapy, including constitutional symptoms, transient laboratory abnormalities (e.g., electrolytes, liver function tests, and coagulation tests), transient hypertension or hypotension, selected skin toxicities (ulceration/rashes in the diaper area, petechiae/purpura), and tumor lysis syndrome. The major toxicities that were attributable to lestaurtinib during previous clinical trials in children and adults have included nausea and vomiting (primarily in adults), and asymptomatic, transient transaminase elevation (primarily in children).

Since toxicities that cause therapy omissions or delays are the most significant in terms of potentially compromising patient outcome, and are the most relevant to the determination of whether the addition of a novel agent to a chemotherapy regimen is "tolerable", we will use this criterion as the basis for a definition of lestaurtinib-related DLT. With a few exceptions, post-Induction toxicities of sufficient severity to cause prolonged (greater than 1 week) omissions or delays in therapy on P9407 Cohort 3 were uncommon. Exceptions include: febrile neutropenia/infection, myelosuppression, mucositis and diaper area skin ulceration, where omissions or delays of greater than 1 week were common, but omissions or delays of greater than 2-3 weeks were rare.

A lestaurtinib-related DLT is therefore defined as follows:

- Any Grade 4 non-hematologic (i.e., excluding blood/bone marrow) toxicity that occurs after the first dose of lestaurtinib and is at least possibly related to lestaurtinib, with the following specific exceptions:
  - Febrile neutropenia or infection
  - Fever
  - Metabolic/laboratory abnormalities (see CTCAE v4 category *Investigations)* that resolve to ≤ Grade 2 within:
    - 14 days, for ALT/SGPT, AST/SGOT, alkaline phosphatase
    - 7 days, for amylase, lipase, total bilirubin
    - 48 hours for all others
  - Coagulation abnormalities (see CTCAE v4 category *Investigations)*: INR, PTT or fibrinogen AEs that resolve to ≤ Grade 2 within 48 hours

- Any Grade 3 non-hematologic (i.e., excluding blood/bone marrow) toxicity that occurs after the first dose of lestaurtinib, is at least possibly attributable to lestaurtinib and results in omission or delay of the beginning of the subsequent course of chemotherapy for greater than 7 days, with the following specific exceptions:
  - Febrile neutropenia or infection
  - Mucositis or diaper area skin ulceration must result in omission or delay of the beginning of the subsequent course of chemotherapy for **greater than 14 days** to be considered a DLT

- No hematologic toxicity will be considered a DLT while a patient is receiving scheduled doses of lestaurtinib. After completion of a lestaurtinib course, persistent Grade 3 or greater neutrophils and/or platelets that results in a **greater than 21 day delay** in the start of the following course of chemotherapy will be considered a DLT (unless the delay in neutrophil or platelet recovery is due to another clearly identifiable factor such as leukemic relapse or documented myelosuppressive infection).

The definitions of lestaurtinib-related DLTs are based in part on the duration of delays in the beginning of subsequent courses of chemotherapy. If the *actual* start date is later than the *expected* start date as listed in the table below, then the course would be *delayed* by the difference between the actual and expected start dates.

Course	Expected Start Date
Re-Induction (Week 10 VCR/DAUN/CPM/PEG-ASP)	21 days AFTER Week 8, Day 15
Consolidation (Week 13 HD MTX)	28 days AFTER Week 10, Day 1
Consolidation (Week 17 HD ARAC/PEG-ASP)	21 days AFTER Week 15, Day 15
Continuation I (Week 20 VCR/DEX)	21 days AFTER Week 17, Day 29
Continuation I (Week 27 ETOP/CPM)	21 days AFTER Week 24, Day 1
Continuation I (Week 30 HD ARAC/PEG-ASP)	21 days AFTER Week 27, Day 22
Continuation I (Week 40 ETOP/CPM)	21 days AFTER Week 37, Day 1
Continuation I (Week 43 HD ARAC/PEG-ASP)	21 days AFTER Week 40, Day 22

NOTE: During the safety/efficacy phase, a study co-chair should be notified in the event of a suspected lestaurtinib-related DLT.

4.2.3 Determining a Safe and Active Dose of Lestaurtinib

The safety/activity phase will proceed with independent arms for IR and HR patients. The presence or absence of a DLT will be determined for each patient during the first 2 courses of lestaurtinib (i.e., during the Induction Intensification and Re-Induction phases). Cohorts of 5 patients will be enrolled in each of the 2 strata (i.e., < 90 days and ≥ 90 days) at the starting dose level 1 (DL1). Any patient who experiences a DLT after receiving at least one dose of lestaurtinib on study will be considered evaluable for toxicity of lestaurtinib. A patient will be considered inevaluable for toxicity of lestaurtinib and will be replaced if he/she is: (1) removed from protocol therapy for a reason other than a DLT prior to receiving at least 75% of the prescribed lestaurtinib doses during the first 2 courses of lestaurtinib (i.e., during the Induction Intensification and Re-Induction phases); or (2) does not experience a DLT and receives less than 75% of the prescribed lestaurtinib doses during the first 2 courses of lestaurtinib (i.e., during the Induction Intensification and Re-Induction phases). As each patient proceeds through treatment on and recovery from Induction Intensification and Re-Induction, rapid reporting via eRDES of toxicity data and actual number of prescribed lestaurtinib doses received will be required. After the fifth evaluable patient in a cohort recovers from the Re-Induction phase (i.e., the patient is ready to begin Consolidation/Week 13), toxicity data will be finalized for that cohort. The study committee will then convene a formal conference call review and will make a consensus decision regarding dose changes as shown in the schematic in Section 4.2.1. Accrual to the study will continue between the time the fifth patient of a cohort enrolls and when the committee decision on dose adjustment has been made. IR and HR patients who enroll during these periods of toxicity evaluation for their respective arms will receive chemotherapy only as detailed in Section 4.6.

Once a tolerable dose has been identified for an arm, the study will proceed to the efficacy phase for that arm at that dose level *only if* adequate FLT3 inhibitory plasma levels have been achieved in at least 3 of the patients treated at that dose level (for each patient, "adequate" will be defined as ≥ 90% FLT3 PIA in a majority of available trough samples – see Section 14.0 for details). If DL0 or DL1 is the MTD and adequate FLT3 inhibitory activity is not seen, then the study of lestaurtinib will stop for that arm. If DL2 is well-tolerated but adequate FLT3 inhibitory activity is not seen, then consideration will be given to amending the trial for that arm to allow further dose escalation. If DL0 is not tolerated but adequate FLT3 inhibitory activity is seen, then consideration will be given to amending the trial for that arm to allow further dose de-escalation.

It is expected that the IR stratum will accrue faster than the HR stratum, and will therefore proceed to the randomized phase first (assuming a tolerable and active dose of lestaurtinib is identified). If a tolerable and active dose cannot be identified for the IR stratum, the study will close, since the small number of patients in the HR stratum would be insufficient to power the efficacy phase. If, on the other hand, a tolerable and active dose can be identified for the IR cohort, but not for the HR cohort, the study of

lestaurtinib will continue with the IR stratum only until accrual goals (n = 162 evaluable MLL-R infants) are met.

Note: as of 01/28/11 the safety/activity phase for Intermediate Risk patients was completed, and the randomized efficacy phase began at DL2 (5 mg/kg/day).

Note: as of 02/03/12, the safety/activity phase for High Risk patients was completed, and the randomized efficacy phase began at DL2 (4.25 mg/kg/day).

4.3 Efficacy Phase

Prior to Amendment #5:

IR and HR patients will be eligible for the randomized efficacy phase once a tolerable and biologically active dose has been identified for their respective stratum. Based on the randomization, patients will be assigned to post-Induction therapy with either chemotherapy alone (see Section 4.6) or chemotherapy plus lestaurtinib (see Section 4.7).

Revised Efficacy Phase as of Amendment #5:

IR and HR patients (at institutions in the US and Canada) will be eligible for the lestaurtinib efficacy phase. Patients will be non-randomly assigned to post-Induction therapy with chemotherapy plus lestaurtinib (see Section 4.7).

Arm C Continuation II Updates:

Lestaurtinib will no longer be administered with Continuation II therapy as of Amendment #5. All newly enrolled patients and patients that have not yet reached Continuation II will cease lestaurtinib treatment following Continuation I. Patients currently receiving Continuation II as of Amendment #5 will cease lestaurtinib as of the activation of the amendment.

Note: as of 01/28/11 the safety/activity phase for Intermediate Risk patients was completed, and the randomized efficacy phase began at DL2 (5 mg/kg/day).

Note: as of 02/01/12, the safety/activity phase for High Risk patients was completed, and the randomized efficacy phase began at DL2 (4.25 mg/kg/day).

4.4 Induction Chemotherapy: Weeks 1-5

All patients will receive the same Induction chemotherapy with regard to agents and schedule; however, patients ≥ 7 days and < 6 months old at diagnosis will receive an 11% dose reduction for all non-intrathecal agents (see Section 4.4.2 below) and patients < 7 days old at diagnosis will receive an additional 25% dose reduction for all non-intrathecal agents (see Section 4.4.3 below).

4.4.1 Induction Chemotherapy for Patients ≥ 6 Months Old at Diagnosis

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.125 mg/m^2/dose on Days 8, 15, 22 and 29

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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

DAUNOrubicin: IV over 30 minutes
22.5 mg/m^2/dose Days 8 & 9

***E. coli* L-asparaginase (e.g., Elspar, Kidrolase):** IM
7500 International units/m^2/dose on Days 15, 18, 22, 25, 29 and 33

If *E.coli* L-asparaginase (i.e., Elspar or Kidrolase) is not available, please use Erwinia asparaginase (Erwinaze) as follows:
***Erwinia* L-asparaginase (Erwinaze):** IM
30,000 International units/m^2/dose on Days 15, 18, 22, 25, 29 and 33

PredniSONE: PO/NG
45 mg/m^2/day divided TID on Days 1-7
Give methylprednisolone IV at 80% of the prednisone dose, if needs to be given IV instead of PO/NG

Dexamethasone: PO/NG/IV
4.5 mg/m^2/day divided TID on Days 8-28

Cytarabine: IV over 30 minutes
56.25 mg/m^2/dose Days 8-21

Intrathecal Chemotherapy: IT
Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)

Age-based dosing:

Day 1*	MTX only	< 1 year MTX: 6 mg	≥ 1 year MTX: 8 mg
Day 15	HC and ARAC	< 1 year HC: 12 mg ARAC: 15 mg	≥ 1 year HC: 16 mg ARAC: 20 mg
Day 29	MTX and HC	< 1 year MTX: 6 mg HC: 12 mg	≥ 1 year MTX: 8 mg HC: 16 mg

** Day 1 IT treatment may be given at the time of the diagnostic lumbar puncture.*

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration.

4.4.2 Induction Chemotherapy for Patients ≥ 7 Days and < 6 Months Old at Diagnosis

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1 mg/m^2/dose on Days 8, 15, 22 and 29

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."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

DAUNOrubicin: IV over 30 minutes
20 mg/m^2/dose Days 8 and 9

***E. coli* L-asparaginase (e.g., Elspar, Kidrolase):** IM
6675 International units/m^2/dose on Days 15, 18, 22, 25, 29 and 33

If *E.coli* L-asparaginase (i.e., Elspar or Kidrolase) is not available, please use Erwinia asparaginase (Erwinaze) as follows:
***Erwinia* L-asparaginase (Erwinaze):** IM
27,000 International units/m^2/dose on Days 15, 18, 22, 25, 29 and 33

PredniSONE: PO/NG
40 mg/m^2/day divided TID on Days 1-7
Give methylprednisolone IV at 80% of the prednisone dose, if needs to be given IV instead of PO/NG

Dexamethasone: PO/NG/IV
4 mg/m^2/day divided TID on Days 8-28

Cytarabine: IV over 30 minutes
50 mg/m^2/dose Days 8-21

Intrathecal Chemotherapy: IT
Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)

Day 1*	MTX only	MTX: 6 mg
Day 15	HC and ARAC	HC: 12 mg ARAC: 15 mg
Day 29	MTX and HC	MTX: 6 mg HC: 12 mg

***** *Day 1 IT treatment may be given at the time of the diagnostic lumbar puncture.*

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration.

4.4.3 Induction Chemotherapy for Patients < 7 Days Old at Diagnosis

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
0.75 mg/m^2/dose on Days 8, 15, 22 and 29

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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

DAUNOrubicin: IV over 30 minutes
15 mg/m^2/dose Days 8 and 9

***E. coli* L-asparaginase (e.g., Elspar, Kidrolase):** IM
5000 International units/m^2/dose on Days 15, 18, 22, 25, 29 and 33

If *E.coli* L-asparaginase (i.e., Elspar or Kidrolase) is not available, please use Erwinia asparaginase (Erwinaze) as follows:
***Erwinia* L-asparaginase (Erwinaze):** IM
20,000 International units/m^2/dose on Days 15, 18, 22, 25, 29 and 33

PredniSONE: PO/NG
30 mg/m^2/day divided TID on Days 1-7
Give methylprednisolone IV at 80% of the prednisone dose, if needs to be given IV instead of PO/NG

Dexamethasone: PO/NG/IV
3 mg/m^2/day divided TID on Days 8-28

Cytarabine: IV over 30 minutes
37.5 mg/m^2/dose Days 8-21

Intrathecal Chemotherapy: IT
Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)

Day 1*	MTX only	MTX: 6 mg
Day 15	HC and ARAC	HC: 12 mg ARAC: 15 mg
Day 29	MTX and HC	MTX: 6 mg HC: 12 mg

***** *Day 1 IT treatment may be given at the time of the diagnostic lumbar puncture.*

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration.

The therapy delivery maps (TDMs) for Induction are on the next 3 pages. The TDM numbered 4.4.4 is for patients ≥ 6 months old at diagnosis; the TDM numbered 4.4.5 is for patients ≥ 7 days and < 6 months old at diagnosis; the TDM numbered 4.4.6 is for patients < 7 days old at diagnosis.

Following completion of Induction, the next course (Induction Intensification, Section 4.5.1 or 4.6.1 or 4.7.1) starts on Day 36 or when counts recover and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less (whichever occurs later).

4.4.4 **Induction (for patients ≥ 6 months old at diagnosis)**
Induction lasts 5 weeks (35 days); this Therapy Delivery Map is on **one (1)** page.

Patient name or initials _____ DOB _____

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.125 mg/m²/dose	Days 8, 15, 22, 29	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/T bili d. CSF cell count, cytospin e. Serum IgG f. Echo or MUGA g. CrCl or GFR h. Local BM eval i. BM per AALL08B1 j. PB for Lestaurtinib PK/PIA (see Section 13.1 for details) k. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
DAUNOrubicin (DAUN)	IV over 30 min	22.5 mg/m²/dose	Days 8 & 9		
E. coli L-asparginase (*E. coli* L-ASP)	IM	7500 International units/m²/dose	Days 15, 18, 22, 25, 29, 33	***Erwinia* L-asparaginase (Erwinaze):** 30,000 International units/m²/dose	
PrednISONE (PRED)	PO/NG (may give IV)	45 mg/m² divided TID	Days 1-7	See Section 4.4.1 for IV administration guidelines	
Dexamethasone (DEX)	PO/NG (may give IV)	4.5 mg/m² divided TID	Days 8-28		
Cytarabine (ARAC)	IV over 30 min	56.25 mg/m²/dose	Days 8-21		
Intrathecal Therapy: Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 6 mg, HC: 12 mg, ARAC: 15 mg ≥ 1: MTX: 8 mg, HC: 16 mg, ARAC: 20 mg	Days 1*: MTX only Day 15: HC & ARAC Day 29: MTX & HC	**Note age-based dosing** * Day 1 IT MTX may be given at the time of diagnostic lumbar puncture See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	

Therapy Delivery Map **Ht____cm** **Wt_____kg** **BSA_____m²**

Date Due	Date Given	Week	Day	VCR ____mg	DAUN ____mg	L-ASP ____IU	PRED ___mg ___mg ___mg	DEX ___mg ___mg ___mg	ARAC ____mg	IT Therapy ___mg (MTX) ___mg (HC) ___mg (ARAC)	Studies
				Enter calculated dose above and actual dose administered below							
		1	1*				___mg ___mg ___mg			___mg (MTX)	(a, b, c, d, e, f, g, h, i, j, k)^
			2				___mg ___mg ___mg				
			3				___mg ___mg ___mg				
			4				___mg ___mg ___mg				
			5				___mg ___mg ___mg				
			6				___mg ___mg ___mg				
			7				___mg ___mg ___mg				
		2	8	____mg	____mg			___mg ___mg ___mg	____mg		b
			9		____mg			___mg ___mg ___mg	____mg		
			10					___mg ___mg ___mg	____mg		
			11					___mg ___mg ___mg	____mg		
			12					___mg ___mg ___mg	____mg		
			13-14					___mg ___mg ___mg	____mg		
		3	15	____mg		____IU		___mg ___mg ___mg	____mg	___mg (HC) ___mg (ARAC)	b, c, d, e
			16					___mg ___mg ___mg	____mg		
			17					___mg ___mg ___mg	____mg		
			18			____IU		___mg ___mg ___mg	____mg		
			19					___mg ___mg ___mg	____mg		
			20-21					___mg ___mg ___mg	____mg		
		4	22	____mg		____IU		___mg ___mg ___mg			b
			23-24					___mg ___mg ___mg			
			25			____IU		___mg ___mg ___mg			
			26-28					___mg ___mg ___mg			
		5	29	____mg		____IU				___mg (MTX) ___mg (HC)	b, c, d, e
			30-32								
			33			____IU					
			36	**Start next course (Induction Intensification, Section 4.5.1 or 4.6.1 or 4.7.1) on Day 36 or when blood count parameters are met and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less (whichever occurs later).**							

Comments may be documented on a separate page.
* Day 1 IT MTX may be given at the time of diagnostic lumbar puncture ^ Pretreatment observations (see Section 7.1) may fulfill Day 1 requirements

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.4.5 **Induction (for patients ≥ 7 days and < 6 months old at diagnosis)**

Induction lasts 5 weeks (35 days); this Therapy Delivery Map (TDM) is on **one (1)** page. This TDM reflects an 11% dose reduction in all non-intrathecal agents due to age < 6 months old at diagnosis.

_____ Patient name or initials _____ DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1 mg/m²/dose	Days 8, 15, 22, 29	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/T bili d. CSF cell count, cytospin e. Serum IgG f. Echo or MUGA g. CrCl or GFR h. Local BM eval i. BM per AALL08B1 j. PB for Lestaurtinib PK/PIA (see Section 13.1 for details) k. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
DAUNOrubicin (DAUN)	IV over 30 min	20 mg/m²/dose	Days 8 & 9		
E. coli L-asparginase (*E. coli* L-ASP)	IM	6675 International units/m²/dose	Days 15, 18, 22, 25, 29, 33	***Erwinia* L-asparaginase (Erwinaze):** 27,000 International units/m²/dose	
PrednISONE (PRED)	PO/NG (may give IV)	40 mg/m²/day divided TID	Days 1-7	See Section 4.4.2 for IV administration guidelines	
Dexamethasone (DEX)	PO/NG (may give IV)	4 mg/m²/day divided TID	Days 8-28		
Cytarabine (ARAC)	IV over 30 min	50 mg/m²/dose	Days 8-21		
Intrathecal Therapy: Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	MTX: 6 mg HC: 12 mg ARAC: 15 mg	Days 1*: MTX only Day 15: HC & ARAC Day 29: MTX & HC	**Note age-based dosing** * Day 1 IT MTX may be given at the time of diagnostic lumbar puncture See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	

Therapy Delivery Map **Ht____ cm** **Wt_____ kg** **BSA_____ m²**

Date Due	Date Given	Week	Day	VCR ____mg	DAUN ____mg	L-ASP ____IU	PRED ___mg ___mg ___mg	DEX ___mg ___mg ___mg	ARAC ____mg	IT Therapy ___mg (MTX) ___mg (HC) ___mg (ARAC)	Studies
				Enter calculated dose above and actual dose administered below							
		1	1*				___mg ___mg ___mg			___mg (MTX)	(a, b, c, d, e, f, g, h, i, j, k)^
			2				___mg ___mg ___mg				
			3				___mg ___mg ___mg				
			4				___mg ___mg ___mg				
			5				___mg ___mg ___mg				
			6				___mg ___mg ___mg				
			7				___mg ___mg ___mg				
		2	8	____mg	____mg			___mg ___mg ___mg	____mg		b
			9		____mg			___mg ___mg ___mg	____mg		
			10					___mg ___mg ___mg	____mg		
			11					___mg ___mg ___mg	____mg		
			12					___mg ___mg ___mg	____mg		
			13-14					___mg ___mg ___mg	____mg		
		3	15	____mg		____IU		___mg ___mg ___mg	____mg	___mg (HC) ___mg (ARAC)	b, c, d, e
			16					___mg ___mg ___mg	____mg		
			17					___mg ___mg ___mg	____mg		
			18			____IU		___mg ___mg ___mg	____mg		
			19					___mg ___mg ___mg	____mg		
			20-21					___mg ___mg ___mg	____mg		
		4	22	____mg		____IU		___mg ___mg ___mg			b
			23-24					___mg ___mg ___mg			
			25			____IU		___mg ___mg ___mg			
			26-28					___mg ___mg ___mg			
		5	29	____mg		____IU				___mg (MTX) ___mg (HC)	b, c, d, e
			30-32								
			33			____IU					
			36	**Start next course (Induction Intensification, Section 4.5.1 or 4.6.1 or 4.7.1) on Day 36 or when blood count parameters are met and mucositis and/or diaper area ulceration ≥ Grade 3 has improved to Grade 2 or less (whichever occurs later).**							

Comments may be documented on a separate page.

***** Day 1 IT MTX may be given at the time of diagnostic lumbar puncture ^ Pretreatment observations (see Section 7.1) may fulfill Day 1 requirements

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.4.6 Induction (for patients < 7 days old at diagnosis)

Induction lasts 5 weeks (35 days); this Therapy Delivery Map is on **one (1)** page. This TDM reflects a 25% dose reduction in all non-intrathecal agents due to age < 7 days old at diagnosis.

_____ Patient name or initials _____ DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.75 mg/m^2/dose	Days 8, 15, 22, 29	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/T bili d. CSF cell count, cytospin e. Serum IgG f. Echo or MUGA g. CrCl or GFR h. Local BM eval i. BM per AALL08B1 j. PB for Lestaurtinib PK/PIA (see Section 13.1 for details) k. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
DAUNOrubicin (DAUN)	IV over 30 min	15 mg/m^2/dose	Days 8 & 9		
E. coli L-asparginase (*E. coli* L-ASP)	IM	5000 International units/m^2/dose	Days 15, 18, 22, 25, 29, 33	***Erwinia* L-asparaginase (Erwinaze):** 20,000 International units/m^2/dose	
PrednISONE (PRED)	PO/NG (may give IV)	30 mg/m^2/day divided TID	Days 1-7	See Section 4.4.3 for IV administration guidelines	
Dexamethasone (DEX)	PO/NG (may give IV)	3 mg/m^2/day divided TID	Days 8-28		
Cytarabine (ARAC)	IV over 30 min	37.5 mg/m^2/dose	Days 8-21		
Intrathecal Therapy: Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	MTX: 6 mg HC: 12 mg ARAC: 15 mg	Days 1*: MTX only Day 15: HC & ARAC Day 29: MTX & HC	**Note age-based dosing** * Day 1 IT MTX may be given at the time of diagnostic lumbar puncture See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	

Therapy Delivery Map **Ht____cm** **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Week	Day	VCR ____mg	DAUN ____mg	L-ASP ____IU	PRED ___mg ___mg ___mg	DEX ___mg ___mg ___mg	ARAC ____mg	IT Therapy ___mg (MTX) ___mg (HC) ___mg (ARAC)	Studies
				Enter calculated dose above and actual dose administered below							
		1	1*				___mg ___mg ___mg			___mg (MTX)	(a, b, c, d, e, f, g, h, i, j, k)^
			2				___mg ___mg ___mg				
			3				___mg ___mg ___mg				
			4				___mg ___mg ___mg				
			5				___mg ___mg ___mg				
			6				___mg ___mg ___mg				
			7				___mg ___mg ___mg				
		2	8	____mg	____mg			___mg ___mg ___mg	____mg		b
			9		____mg			___mg ___mg ___mg	____mg		
			10					___mg ___mg ___mg	____mg		
			11					___mg ___mg ___mg	____mg		
			12					___mg ___mg ___mg	____mg		
			13-14					___mg ___mg ___mg	____mg		
		3	15	____mg		____IU		___mg ___mg ___mg	____mg	___mg (HC) ___mg (ARAC)	b, c, d, e
			16					___mg ___mg ___mg	____mg		
			17					___mg ___mg ___mg	____mg		
			18			____IU		___mg ___mg ___mg	____mg		
			19					___mg ___mg ___mg	____mg		
			20-21					___mg ___mg ___mg	____mg		
		4	22	____mg		____IU		___mg ___mg ___mg			b
			23-24					___mg ___mg ___mg			
			25			____IU		___mg ___mg ___mg			
			26-28					___mg ___mg ___mg			
		5	29	____mg		____IU				___mg (MTX) ___mg (HC)	b, c, d, e
			30-32								
			33			____IU					
			36	**Start next course (Induction Intensification, Section 4.5.1 or 4.6.1 or 4.7.1) on Day 36 or when blood count parameters are met and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less (whichever occurs later).**							

Comments may be documented on a separate page.

* Day 1 IT MTX may be given at the time of diagnostic lumbar puncture ^ Pretreatment observations (see Section 7.1) may fulfill Day 1 requirements

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.5 Post-Induction Arm A [for SR Patients (MLL-G)]

To avoid diaper area skin ulceration, especially at Weeks 6 and 7 of HD MTX, please see **Appendix I**, section on Perineal Irritation.

4.5.1 Induction Intensification: Weeks 6-9 (Arm A)

- Begin Induction Intensification when ANC > 750/µL and platelets > 75,000/µL and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less.
- To begin Day 8 HD MTX, mucositis or diaper area skin ulceration ≥ Grade 3 must have improved to Grade 2 or less.

High Dose Methotrexate: IV
200 mg/m^2 IV over 20 minutes THEN 3800 mg/m^2 IV over remainder of 24 hours [4000 mg/m^2 IV in 24 hours] on Days 1 & 8. See Section 5.8 for IV fluid and dose modification guidelines.

Leucovorin rescue: Leucovorin will begin at T=42 hr at the standard dose of 15 mg/m^2/dose IV/PO q6 hours as long as the T=24 hr methotrexate level is < 150µM, and will continue at this dose as long as the T=42 hr and T=48 hr methotrexate levels are < 1µM and < 0.4µM (all timed from the beginning of the methotrexate infusion), respectively. If any of the levels is above these thresholds, then the more detailed guidelines described in Section 5.8 will be followed.

HD MTX Infusion Guidelines:
See Appendix V for a flowchart of the HD MTX/LCV guidelines.

When IT therapy and HD MTX 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 HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM, as well as nonsteroidal anti-inflammatory agents, proton pump inhibitors, aspirin-containing drugs and penicillins.

Infants receiving therapeutic doses of amphotericin should have that drug withheld on the day HD MTX is administered and for the following 24 hours due to the risk of delayed MTX excretion, renal dysfunction and resultant toxicity.

See Appendix I for supportive care guidelines aimed at reducing the risk of perineal irritation associated with HD MTX administration.

Triple Intrathecal Chemotherapy: IT Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC) Days 1 & 8; deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion

Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg HC: 7.5 mg ARAC: 15 mg
≥ 1	MTX: 8 mg HC: 8 mg ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration.

Etoposide: IV over 2 hours
100 mg/m^2/dose on Days 15-19.

Cyclophosphamide: IV over 30 minutes
300 mg/m^2/dose on Days 15-19

Mesna: IV
150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion (CI) IV over 4 hours following each dose of cyclophosphamide (2 total doses per day).

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 20 and until ANC > 1500/µL x 2 days post nadir.
Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

The therapy delivery map (TDM) for Induction Intensification is on the next page.

Following completion of Induction Intensification, the next course (Re-Induction, Section 4.5.2) starts on Day 29 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later). Patients must also be in morphologic remission in order to begin Re-Induction.

4.5.1.1 Induction Intensification (ARM A: SR patients classified as MLL-G)

Modified Induction Intensification is for SR patients (4 weeks/28 days)

_____
Patient name or initials

_____
DOB

*Begin Induction Intensification when ANC > 750/µL and platelets > 75,000/µL and mucositis/diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less. This Course lasts 28 days and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High Dose Methotrexate (HD MTX)	IV	200 mg/m^2 over 20 min THEN 3800 mg/m^2 over remainder 24 hrs	Days 1 & 8*	4000 mg/m^2 total in 24 hrs; see Section 4.5.1 for administration guidelines	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/ AST/ALT/T bili d. Serum IgG e. CSF cell count, diff, cytospin f. Local BM eval g. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	IV/PO	Start 15 mg/m^2/dose q6 hrs @ T=42 hr	Days 2 & 9	See Section 4.5.1 for administration guidelines	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) Dose < 1 MTX: 7.5mg HC: 7.5 mg ARAC: 15 mg ≥ 1 MTX: 8 mg HC: 8 mg ARAC: 16 mg	Days 1 & 8	Deliver ITT within 6 hrs of beginning IV MTX infusion **Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 15-19		
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 15-19		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 15-19	See Section 4.5.1 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. on Day 20	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	

Therapy Delivery Map **Ht____cm** **Wt____kg** **BSA_____m^2**

Date Due	Date Given	Week	Day	HD MTX __mg __mg	LCV ____mg	ITT ___mg (MTX) ___mg (HC) ___mg (ARAC)	ETOP ____mg	CPM ____mg	MESNA ____mg ____mg	G-CSF ___mcg	Studies
				Enter calculated dose above and actual dose administered below							
		6	1	__mg __mg		___mg (MTX) ___mg (HC) ___mg (ARAC)					a, b, c, d, e, f, g
			2		____mg						
			3-7		↓						
		7	8*	(__mg __mg)*		___mg (MTX) ___mg (HC) ___mg (ARAC)					b, e
			9		____mg						
			10-14		↓						
		8	15				_____mg	_____mg	____mg ____mg		b, d
			16				_____mg	_____mg	____mg ____mg		
			17				_____mg	_____mg	____mg ____mg		
			18				_____mg	_____mg	____mg ____mg		
			19				_____mg	_____mg	____mg ____mg		
			20							____mcg	
			21							____mcg	
		9	22-28							____mcg	
			29	**Start next course (Re-Induction, Section 4.5.2) on Day 29 or when blood count parameters are met (whichever occurs later).**							

Indicate last G-CSF if past Day 28 _____

Comments may be documented on a separate page.

* In order to receive Day 8 HD MTX, mucositis or diaper area skin ulceration ≥ Grade 3 must have improved to Grade 2 or less.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.5.2 Re-Induction: Weeks 10-12 (Arm A)

To begin Re-Induction, patients must be in morphologic remission. Patient must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF at least 48 hours

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
0.05 mg/kg on Days 1 & 15 AND 0.03 mg/kg on Day 8

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."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

DAUNOrubicin: IV over 30 minutes
Days 1 & 2

Dose is mg/kg/day based on age at diagnosis:
< 6 months = 1.7 mg/kg/dose
6 months to 8.99 months = 2.1 mg/kg/dose
≥ 9 months = 2.6 mg/kg/dose

Cyclophosphamide: IV over 30 minutes
250 mg/m^2/dose q12 hours x 4 total doses on Days 3 & 4

Mesna: IV
125 mg/m^2/dose with each dose of cyclophosphamide over 30 minutes; then 125 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (4 total doses per day).

Pegaspargase: IM
2500 International units/m^2/dose on Day 4

Dexamethasone: PO/NG/IV
10 mg/m^2/day divided BID on Days 1-7 & 15-21

Triple Intrathecal Chemotherapy: IT Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)
Days 1 & 15 ONLY

Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration.

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 5 and until ANC > 1500/µL x 2 days post nadir.

Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D_5W by IV infusion over 15-30 minutes or by continuous infusion.

The therapy delivery map (TDM) for Re-Induction is on the next page.

Following completion of Re-Induction, the next course (Consolidation, Section 4.5.3) starts on Day 22 or when counts recover, G-CSF has been discontinued for at least 48 hours and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less (whichever occurs later).

4.5.2.1 Re-Induction (ARM A: SR patients classified as MLL-G)

Modified Re-Induction is for SR patients (3 weeks/21 days)

_____ Patient name or initials _____ DOB

*Begin Re-Induction if patient is in morphologic remission; patient must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 21 days and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg on Days 1 & 15 AND 0.03 mg/kg on Day 8@	Days 1, 8@, 15	+ Or infusion via minibag as per institutional policy @ Dose differs on Day 8	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN Cr/AST/ALT/ T bili d. Serum IgG e. CSF cell count, cytospin f. Local BM eval g. Echo or MUGA h. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
DAUNOrubicin (DAUN)	IV over 30 min	< 6 mos. = 1.7 mg/kg/dose 6-8.99 mos.= 2.1 mg/kg/dose ≥ 9 mos. = 2.6 mg/kg/dose	Days 1 & 2	Dosing based on age at diagnosis	
Cyclophosphamide (CPM)	IV over 30 min	250 mg/m²/dose q12 hrs x 4 total doses	Days 3 & 4		
Mesna	IV over 30 min followed by CI	125 mg/m²/dose with CPM followed by 125 mg/m²/dose over 4 hrs (4 total doses/day)	Days 3 & 4	See Section 4.5.2 for infusion details	
Pegaspargase (PEG-ASP)	IM	2500 International units/m²/dose **x 1 dose**	Day 4 ONLY		
Dexamethasone (DEX)	PO/NG/IV	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg, HC: 7.5 mg, ARAC: 15 mg ≥ 1: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg	Days 1 & 15 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. on Day 5; cont. w/o regard to VCR or ITs	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	

Therapy Delivery Map **Ht____cm** **Wt_____kg** **BSA_____m²**

Date Due	Date Given	Week	Day	VCR D1 &15 ____mg D8 ____@	DAUN ____mg	CPM ___mg ___mg	MESNA ___mg ___mg	PEG-ASP ___IU	DEX ___mg ___mg	ITT ___mg (MTX) ___mg (HC) ___mg (ARAC)	G-CSF ___mcg	Studies
				Enter calculated dose above and actual dose administered below								
		10	1	____mg	____mg				___mg ___mg	___mg (MTX) ___mg (HC) ___mg (ARAC)		a, b, c, d, e, f, g, h
			2		____mg				___mg ___mg			
			3			___mg ___mg	___mg ___mg ___mg ___mg		___mg ___mg			
			4			___mg ___mg	___mg ___mg ___mg ___mg	___IU	___mg ___mg			
			5						___mg ___mg		____mcg	
			6						___mg ___mg			
			7						___mg ___mg			
		11	8	____mg@								
			9-14									
		12	15	____mg					___mg ___mg	___mg (MTX) ___mg (HC) ___mg (ARAC)		b, e
			16						___mg ___mg			
			17						___mg ___mg			
			18						___mg ___mg			
			19						___mg ___mg			
			20						___mg ___mg			
			21						___mg ___mg			
			22	**Start next course (Consolidation, Section 4.5.3) on Day 22 or when blood count parameters are met (whichever occurs later).**								

Comments may be documented on a separate page. Indicate last G-CSF if past Day 21 _____

@ Dose differs on Day 8

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.5.3 Consolidation: Weeks 13-19 (Arm A)

- To begin Consolidation, patient must have an ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.
- To begin Consolidation, patient must have recovered from mucositis and/or diaper area skin ulceration ≥ Grade 3.
- To begin Day 15 ETOP/CPM, patient must have ANC > 500/µL and platelets > 50,000/µL
- To begin Day 29 HD ARAC, patient must have an ANC > 500/µL and platelets > 50,000/µL and have been off G-CSF for at least 48 hours.

High Dose Methotrexate: IV
200 mg/m^2 IV over 20 minutes THEN 3800 mg/m^2 IV over remainder of 24 hours [4000 mg/m^2 IV in 24 hours] on Days 1 & 8. See Section 5.8 for IV fluid and dose modification guidelines.

Leucovorin rescue: Leucovorin will begin at T=42 hr at the standard dose of 15 mg/m^2/dose IV/PO q6 hours as long as the T=24 hr methotrexate level is < 150 µM, and will continue at this dose as long as the T=42 hr and T=48 hr methotrexate levels are < 1 µM and < 0.4 µM (all timed from the beginning of the methotrexate infusion), respectively. If any of the levels is above these thresholds, then the more detailed guidelines described in Section 5.8 will be followed.

HD MTX Infusion Guidelines:
See Appendix V for a flowchart of the HD MTX/LCV guidelines.

When IT therapy and HD MTX 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 HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM, as well as nonsteroidal anti-inflammatory agents, proton pump inhibitors, aspirin-containing drugs and penicillins.

Infants receiving therapeutic doses of amphotericin should have that drug withheld on the day HD MTX is administered and for the following 24 hours due to the risk of delayed MTX excretion, renal dysfunction and resultant toxicity.

See Appendix I for supportive care guidelines aimed at reducing the risk of perineal irritation associated with HD MTX administration.

Triple Intrathecal Chemotherapy: IT Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC) Day 1 ONLY; deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion

Age-based dosing:	Age (years)	Dose
	< 1	MTX: 7.5 mg
		HC: 7.5 mg
		ARAC: 15 mg
	≥ 1	MTX: 8 mg
		HC: 8 mg
		ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration.

Etoposide: IV over 2 hours
100 mg/m^2/dose on Days 15-19

Cyclophosphamide: IV over 30 minutes
300 mg/m^2/dose on Days 15-19

Mesna: IV
150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (2 total doses per day).

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 20 & Day 31, continuing until ANC > 1500/µL x 2 days post nadir. Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

High Dose Cytarabine: IV over 3 hours
3000 mg/m^2/dose q12 hrs x 4 doses total on Days 29 & 30, beginning a min of 48 hrs AFTER G-CSF

Pegaspargase: IM
2500 International units/m^2/dose on Day 30 (3 hours after completion of final dose HD ARAC)

The therapy delivery map (TDM) for Consolidation is on the next page.

Following completion of Consolidation, the next course (Continuation I, Section 4.5.4) starts on Day 50 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later).

4.5.3.1 Consolidation (ARM A: SR patients classified as MLL-G)

Modified Consolidation is for SR patients (7 weeks/49 days)

Patient name or initials _____ DOB _____

*Begin Consolidation when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. Patient must also have recovered from mucositis and/or diaper area skin ulceration ≥ Grade 3. This Course lasts 7 weeks (49 days) and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High Dose Methotrexate (HD MTX)	IV	200 mg/m^2 over 20 min THEN 3800 mg/m^2 over remainder 24 hrs	Days 1 & 8	4000 mg/m^2 total in 24 hrs; see Section 4.5.3 for admin guidelines	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. MTX levels* d. Electrolytes/ BUN/Cr/AST/ ALT/T bili e. Serum IgG f. CSF cell count, diff, cytospin * MTX levels to be drawn per protocol with each dose of HD MTX **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	IV/PO	Start 15 mg/m^2/dose q6 hrs @ T=42 hr	Days 2 & 9	See Section 4.5.3 for administration guidelines	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg, HC: 7.5 mg, ARAC: 15 mg ≥ 1: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg	Day 1 ONLY	Deliver ITT within 6 hrs of beginning IV MTX infusion **Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 15-19	See below for criteria to begin ETOP/CPM	
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 15-19		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 15-19	See Section 4.5.3 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Days 20 & 31	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	3000 mg/m^2/dose q12 hrs x 4 doses; begin min 48 hrs after G-CSF	Days 29 & 30	See below for criteria to begin HD ARAC; see Section 6.4 regarding administration of eye drops	
Pegaspargase (PEG-ASP)	IM	2500 International units/m^2/dose	Day 30	Admin 3 hrs after final HDARAC	

Therapy Delivery Map **Ht____cm** **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Week	Day	HD MTX _____mg	LCV ____mg	ITT ____mg (MTX) ____mg (HC) ____mg(ARAC)	ETOP ____mg	CPM _____mg	MESNA ___mg ___mg	G-CSF ____mcg	HD ARAC ___mg ___mg	PEG-ASP _____IU	Studies
				Enter calculated dose above and actual dose administered below									
		13	1	_____mg		____mg (MTX) ____mg (HC) ____mg (ARAC)							a, b, c, d, e, f
			2		____mg								
			3-7		↓								
		14	8	_____mg									c
			9		____mg								
			10-14		↓								
		15	15**				____mg	_____mg	___mg ___mg				b, d
			16				____mg	_____mg	___mg ___mg				
			17				____mg	_____mg	___mg ___mg				
			18				____mg	_____mg	___mg ___mg				
			19				____mg	_____mg	___mg ___mg				
			20							_____mcg			
			21							↓			
		16	22										
			23										
			24										
			25										
			26										
			27										
			28										
		17	29**								___mg ___mg		b
			30								___mg ___mg	____IU	
			31-35							_____mcg			
		18	36							↓			
			37-42										
		19	43										
			44-49										
			50	**Start next course (Continuation I, Section 4.5.4) on Day 50 or when blood count parameters are met (whichever occurs later).**									

Comments may be documented on a separate page. Indicate last G-CSF if past Day 49 _____

** To begin Day 15 ETOP/CPM and Day 29 HD ARAC therapy, pt must have ANC > 500/µL and plts > 50,000/µL and been off G-CSF for at least 48 hrs

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.5.4 Continuation I: Weeks 20-41 (Arm A)

- To begin Continuation I, patients must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.
- For Weeks 21-23, 25-27, 32-34 & 36-38 IV MTX/MP: Skip week if ANC < 500/µL or platelets < 50,000/µL.
- For Weeks 24 & 35: Begin regardless of counts 4 weeks after the start of Week 20 or 31.
- For Week 31: Begin regardless of counts once off G-CSF for at least 48 hours.
- For Weeks 28 & 39: Begin when ANC > 750/µL and platelets > 75,000/µL.

CYCLE #1: (Weeks 20-30)

Week 20 **VinCRIStine:** 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5
Triple Intrathecal Therapy: Day 1 ONLY [Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)]
Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Weeks 21-23 **Methotrexate:** 20 mg/m^2/dose IV push weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Week 24 **VinCRIStine:** 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5
Triple Intrathecal Therapy: Day 1 ONLY [Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)]
Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Weeks 25-27 **Methotrexate:** 20 mg/m^2/dose IV push weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Week 28 **Etoposide:** 100 mg/m^2/dose IV over 2 hours Days 1-5
Cyclophosphamide: 300 mg/m^2/dose IV over 30 minutes Days 1-5
Mesna: 150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (2 total doses per day)
Filgrastim: 5 mcg/kg/dose SubQ daily beginning Day 6, until ANC > 1500/µL x 2 days post nadir. Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

Weeks 29-30 REST
Continue G-CSF until ANC > 1500/µL x 2 days post nadir

CYCLE #2: (Weeks 31-41) **Patient must be off G-CSF for at least 48 hours**

Weeks 31-41 Repeat Cycle #1

The therapy delivery maps (TDMs) for Continuation I are on the next two (2) pages.

Following completion of Continuation I, the next course (Continuation II, Section 4.5.5) starts the day after Week 41/Day 77 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later).

4.5.4.1 Continuation I (ARM A: SR patients classified as MLL-G)

Modified Continuation I is for SR patients (22 weeks/154 days). Continuation I occurs in two cycles. Each cycle is 11 weeks [9 weeks therapy & 2 weeks rest/recovery]. Cycle #1 includes the therapy described below and is repeated during Cycle #2.

_____
Patient name or initials

_____
DOB

*Begin Continuation I when ANC > 750/µL and platelets > 75,000/µL and patient has been off G-CSF for at least 48 hrs. This Course lasts 154 days; this Therapy Delivery Map is on **two (2)** pages.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg/dose	Days 1 & 29	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN/Cr/ AST/ALT/T bili d. Serum IgG e. CrCl or GFR f. CSF cell count, diff, cytospin g. Local BM eval h. *OPTIONAL BM for flow MRD, molec. MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m^2/dose BID	Days 1-5 & 29-33	Total daily dose: 6 mg/m^2/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) Dose < 1 MTX: 7.5mg HC: 7.5 mg ARAC: 15 mg ≥ 1 MTX: 8 mg HC: 8 mg ARAC: 16 mg	Days 1 & 29	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (IV MTX)	IV push	20 mg/m^2/dose	Days 8, 15, 22, 36, 43, 50		
Mercaptopurine (MP)	PO/NG	75 mg/m^2/dose See Appendix VI for dosing.	Days 8-28 & 36-56	Should be given on an empty stomach	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 57-61		
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 57-61		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 57-61	See Section 4.5.4 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Day 62	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	

Circle Cycle #: 1 2 **Ht____cm** **Wt____kg** **BSA____m^2**

Date Due	Date Given	Week	Day	VCR ____mg	DEX ___mg ___mg	ITT ____mg (MTX) ____mg (HC) ____mg (ARAC)	IV MTX ____mg	MP ____mg	Studies
				Enter calculated dose above and actual dose administered below					
		20/(31)α	1	____mg	___mg ___mg	____mg (MTX) ____mg (HC) ____mg (ARAC)			a*, b, c, d, e*, f, (g, h)*
			2		___mg ___mg				
			3		___mg ___mg				
			4		___mg ___mg				
			5		___mg ___mg				
			6-7						
		(21/32)β	8				___mg	____mg	b
			9-14					↓	
		(22/33)β	15				___mg		b
			16-21						
		(23/34)β	22				___mg		b
			23-28						
		(24/35)γ	29	____mg	___mg ___mg	____mg (MTX) ____mg (HC) ____mg (ARAC)			b, d, f
			30		___mg ___mg				
			31		___mg ___mg				
			32		___mg ___mg				
			33		___mg ___mg				

Comments may be documented on a separate page.

α Begin regardless of counts once off G-CSF for at least 48 hours

β For IV MTX/MP: skip week if ANC < 500/µL or platelets < 50,000/µL

γ Begin regardless of counts 4 weeks after the start of Week 20/31

* Week 20 (Cycle #1) ONLY

4.5.4.1 Continuation I (ARM A: SR patients classified as MLL-G)

Modified Continuation I is for SR patients (22 weeks/154 days). Continuation I occurs in two cycles. Each cycle is 11 weeks [9 weeks therapy & 2 weeks rest/recovery]. Cycle #1 includes the therapy described below and is repeated during Cycle #2.

_____
Patient name or initials

_____
DOB

*Begin Continuation I when ANC > 750/µL and platelets > 75,000/µL and patient has been off G-CSF for at least 48 hrs. This Course lasts 154 days; this Therapy Delivery Map is on **two (2)** pages.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg/dose	Days 1 & 29	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN/ Cr/AST/ALT/ T bili d. Serum IgG e. CrCl or GFR f. CSF cell count, diff, cytospin g. Local BM eval h. *OPTIONAL BM for flow MRD, molec. MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m^2/dose BID	Days 1-5 & 29-33	Total daily dose: 6 mg/m^2/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) Dose < 1 MTX: 7.5mg HC: 7.5 mg ARAC: 15 mg ≥ 1 MTX: 8 mg HC: 8 mg ARAC: 16 mg	Days 1 & 29	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (IV MTX)	IV push	20 mg/m^2/dose	Days 8, 15, 22, 36, 43, 50		
Mercaptopurine (MP)	PO/NG	75 mg/m^2/dose See Appendix VI for dosing.	Days 8-28 & 36-56	Should be given on an empty stomach	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 57-61	See Section 4.5.4 for criteria to begin ETOP/CPM	
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 57-61		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 57-61	See Section 4.5.4 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Day 62	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	

Circle Cycle #: 1 2 **Ht____cm** **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Week	Day	IV MTX ___mg	MP ___mg	ETOP ___mg	CPM ___mg	MESNA ___mg ___mg	G-CSF ___mcg	Studies
				Enter calculated dose above and actual dose administered below						
		(25/36)$^\alpha$	36	___mg	___mg					b
			37-42							
		(26/37)$^\alpha$	43	___mg						b
			44-49							
		(27/38)$^\alpha$	50	___mg						d*, b
			51-56							
		(28/39)$^\beta$	57			___mg	___mg	___mg ___mg		b
			58			___mg	___mg	___mg ___mg		
			59			___mg	___mg	___mg ___mg		
			60			___mg	___mg	___mg ___mg		
			61			___mg	___mg	___mg ___mg		
			62						___mcg	
			63						___mcg	
		29/40	64-70						___mcg	b
		30/41	71-77						___mcg	b
			78	*Start Cycle #2 when patient is off G-CSF for at least 48 hrs.*						
				Start next course (Continuation II, Section 4.5.5) the day after Week 41/Day 77 or when blood count parameters are met (whichever occurs later).						

Comments may be documented on a separate page. Indicate last G-CSF if past Day 78/155 _____

$^\alpha$ For IV MTX/MP: skip week if ANC < 500/µL or platelets < 50,000/µL $^\beta$ Begin when ANC > 750/µL and plts > 75,000/µL

***** Week 38 (Cycle #2) ONLY

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.5.5 Continuation II: Weeks 42-104 (Arm A)

To begin Continuation II, patients must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.

Each cycle of Continuation II lasts 12 weeks and should be repeated until 2 calendar years from diagnosis.

Week 42

VinCRIStine: 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5
IT Methotrexate: < 1 year: 7.5 mg Day 1 ONLY
1 year - < 2 years: 8 mg Day 1 ONLY
≥ 2 years: 10 mg Day 1 ONLY
See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration

Weeks 43-45

Methotrexate: 20 mg/m^2/dose PO/NG weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Week 46

VinCRIStine: 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5

Weeks 47-49

Methotrexate: 20 mg/m^2/dose PO/NG weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Continue repeating 12 week cycles until 2 years from diagnosis (see below for remaining cycle information)

Week 50

VinCRIStine: 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5

Weeks 51-53

Methotrexate: 20 mg/m^2/dose PO/NG weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Continue repeating 12 week cycles until 2 years from diagnosis (see above for Week 42-49)

The therapy delivery map (TDM) for Continuation II is on the next page.

4.5.5.1 Continuation II (ARM A: SR patients classified as MLL-G)

Modified Continuation II is for SR patients (12 week cycles repeated until 2 years from diagnosis). Each cycle is 12 weeks in length and includes the therapy described below.

_____
Patient name or initials

_____
DOB

*Begin Continuation II when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course is composed of 12-week cycles that are repeated until 2 calendar years from diagnosis; this Therapy Delivery Map describes one cycle and is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	0.05 mg/kg/dose	Days 1, 29, 57	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN/Cr/AST /ALT/T bili d. Serum IgG e. CSF cell count, diff, cytospin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m²/dose BID	Days 1-5, 29-33, 57-61	Total daily dose: 6 mg/m²/day, divided BID	
Intrathecal Methotrexate (IT MTX)	IT	Age (years) Dose < 1 7.5 mg 1 - < 2 8 mg ≥ 2 10 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (MTX)	PO/NG	20 mg/m²/dose	Days 8, 15, 22, 36, 43, 50, 64, 71, 78	Hold with IT MTX	
Mercaptopurine (MP)	PO/NG	75 mg/m²/dose See Appendix VI for dosing.	Days 8-28, 36-56, 64-84	Should be given on an empty stomach	

Cycle #_____ Ht____cm Wt_____kg BSA_____m²

Date Due	Date Given	Week	Day	VCR _____mg	DEX ___mg ___mg	IT MTX _____mg	PO MTX _____mg	MP _____mg	Studies
				Enter calculated dose above and actual dose administered below					
		42	1	_____mg	___mg ___mg	_____mg			(a, c, d, e)*, b
			2						
			3						
			4						
			5						
			6-7						
		43	8				____mg	_____mg	
			9-14						
		44	15				____mg		
			16-21						
		45	22				____mg		
			23-28						
		46	29	_____mg	___mg ___mg				b
			30						
			31						
			32						
			33						
		47	36				____mg	_____mg	
			37-42						
		48	43				____mg		
			44-49						
		49	50				____mg		
			51-56						
		50	57	_____mg	___mg ___mg				b
			58						
			59						
			60						
			61						
			62-63						
		51	64				____mg	_____mg	
			65-70						
		52	71				____mg		
			72-77						
		53	78				____mg		
			79-84						
			End of Therapy						

Comments may be documented on a separate page. * Start of each 12-week cycle

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.6 Post-Induction Arm B [Chemotherapy ONLY for IR/HR Patients (MLL-R)] *(RETIRED)*

To avoid diaper area skin ulceration, especially at Weeks 6 and 7 of HD MTX, please see **Appendix I**, section on Perineal Irritation.

4.6.1 Induction Intensification: Weeks 6-9 (Arm B)

- Begin Induction Intensification when ANC > 750/µL and platelets > 75,000/µL and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less.
- To begin Day 8 HD MTX, mucositis or diaper area skin ulceration ≥ Grade 3 must have improved to Grade 2 or less.

High Dose Methotrexate: IV
200 mg/m^2 IV over 20 minutes THEN 3800 mg/m^2 IV over remainder of 24 hours [4000 mg/m^2 IV in 24 hours] on Days 1 & 8. See Section 5.8 for IV fluid and dose modification guidelines.

Leucovorin rescue: Leucovorin will begin at T=42 hr at the standard dose of 15 mg/m^2/dose IV/PO q6 hours as long as the T=24 hr methotrexate level is < 150 µM, and will continue at this dose as long as the T=42 hr and T=48 hr methotrexate levels are < 1 µM and < 0.4 µM (all timed from the beginning of the methotrexate infusion), respectively. If any of the levels is above these thresholds, then the more detailed guidelines described in Section 5.8 will be followed.

HD MTX Infusion Guidelines:
See Appendix V for a flowchart of the HD MTX/LCV guidelines.

When IT therapy and HD MTX 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 HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM, as well as nonsteroidal anti-inflammatory agents, proton pump inhibitors, aspirin-containing drugs and penicillins.

Infants receiving therapeutic doses of amphotericin should have that drug withheld on the day HD MTX is administered and for the following 24 hours due to the risk of delayed MTX excretion, renal dysfunction and resultant toxicity.

See Appendix I for supportive care guidelines aimed at reducing the risk of perineal irritation associated with HD MTX administration.

Triple Intrathecal Chemotherapy: IT Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)

Days 1 & 8; deliver the IT therapy within 6 hrs of the beginning of the IV MTX infusion

Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Etoposide: IV over 2 hours
100 mg/m^2/dose on Days 15-19

Cyclophosphamide: IV over 30 minutes
300 mg/m^2/dose on Days 15-19

Mesna: IV
150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion (CI) IV over 4 hours following each dose of cyclophosphamide (2 total doses per day).

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 20 and until ANC > 1500/µL x 2 days post nadir. Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

The therapy delivery map (TDM) for Induction Intensification is on the next page.

Following completion of Induction Intensification, the next course (Re-Induction, Section 4.6.2) starts on Day 29 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later). Patients must also be in morphologic remission in order to begin Re-Induction.

4.6.1.1 **Induction Intensification (ARM B: IR/HR patients classified as MLL-R) *(RETIRED)***

Modified Induction Intensification is for IR/HR patients (4 weeks/28 days)

Patient name or initials

DOB

*Begin Induction Intensification when ANC > 750/µL and platelets > 75,000/µL and mucositis/diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less. This Course lasts 28 days and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High Dose Methotrexate (HD MTX)	IV	200 mg/m^2 over 20 min THEN 3800 mg/m^2 over remainder 24 hrs	Days 1 & 8*	4000 mg/m^2 total in 24 hrs; see Section 5.8 for administration guidelines	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/T bili d. Serum IgG e. CSF cell count, diff, cytospin f. Local BM eval g. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	IV/PO	Start 15 mg/m^2/dose q6 hrs @ T=42 hr	Days 2 & 9	See Section 5.8 for administration guidelines	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) Dose < 1 MTX: 7.5mg, HC: 7.5 mg, ARAC: 15 mg ≥ 1 MTX: 8 mg, HC: 8 mg, ARAC: 16 mg	Days 1 & 8	Deliver ITT within 6 hrs of beginning IV MTX infusion **Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 15-19		
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 15-19		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 15-19	See Section 4.6.1 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. on Day 20	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	

Therapy Delivery Map **Ht____cm** **Wt____kg** **BSA_____m^2**

Date Due	Date Given	Week	Day	HD MTX __mg __mg	LCV ____mg	ITT ___mg (MTX) ___mg (HC) ___mg (ARAC)	ETOP _____mg	CPM _____mg	MESNA ____mg ____mg	G-CSF ____mcg	Studies
				Enter calculated dose above and actual dose administered below							
		6	1	__mg __mg		___mg (MTX) ___mg (HC) ___mg (ARAC)					a, b, c, d, e, f, g
			2		____mg						
			3-7		↓						
		7	8*	(__mg __mg)*		___mg (MTX) ___mg (HC) ___mg (ARAC)					b, e
			9		____mg						
			10-14		↓						
		8	15				____mg	____mg	____mg ____mg		b, d
			16				____mg	____mg	____mg ____mg		
			17				____mg	____mg	____mg ____mg		
			18				____mg	____mg	____mg ____mg		
			19				____mg	____mg	____mg ____mg		
			20							____mcg	
			21							↓	
		9	22								
			23-28								
			29	**Start next course (Re-Induction, Section 4.6.2) on Day 29 or when blood count parameters are met (whichever occurs later)**							

Indicate last G-CSF if past Day 28 _____

Comments may be documented on a separate page.

* To receive Day 8 HD MTX, mucositis or diaper area skin ulceration ≥ Grade 3 must have improved to Grade 2 or less

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.6.2 Re-Induction: Weeks 10-12 (Arm B) ***(RETIRED)***

To begin Re-Induction, patients must be in morphologic remission to proceed with therapy. Patient must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF at least 48 hours.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
0.05 mg/kg on Days 1 & 15 AND 0.03 mg/kg on Day 8

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."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

DAUNOrubicin: IV over 30 minutes
Days 1 & 2

Dose is mg/kg/day based on age at diagnosis:
< 6 months = 1.7 mg/kg/dose
6 months to 8.99 months = 2.1 mg/kg/dose
≥ 9 months = 2.6 mg/kg/dose

Cyclophosphamide: IV over 30 minutes
250 mg/m^2/dose q12 hours x 4 doses total on Days 3 & 4

Mesna: IV
125 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 125 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (4 total doses per day).

Pegaspargase: IM
2500 International units/m^2/dose on Day 4

Dexamethasone: PO/NG/IV
10 mg/m^2/day divided BID on Days 1-7 & 15-21

Triple Intrathecal Chemotherapy: IT
Days 1 & 15 ONLY

Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 5 and until ANC > 1500/µL x 2 days post nadir
Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

The therapy delivery map (TDM) for Re-Induction is on the next page.

Following completion of Re-Induction, the next course (Consolidation, Section 4.6.3) starts on Day 22 or when counts recover, G-CSF has been discontinued for at least 48 hours and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less (whichever occurs later).

4.6.2.1 Re-Induction (ARM B: IR/HR patients classified as MLL-R)

(RETIRED) Modified Re-Induction is for IR/HR patients (3 weeks/21 days)

Patient name or initials _____ DOB _____

*Begin Re-Induction if patient is in morphologic remission; patient must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 21 days and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg on Days 1 & 15 AND 0.03 mg/kg on Day 8@	Days 1, 8@, 15	+ Or infusion via minibag as per institutional policy @ Dose differs on Day 8	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/ T bili d. Serum IgG e. CSF cell count, cytospin f. Local BM eval g. Echo or MUGA h. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
DAUNOrubicin (DAUN)	IV over 30 min	Age at diagnosis: < 6 mos. = 1.7 mg/kg/dose 6-8.99 mos.= 2.1 mg/kg/dose ≥ 9 mos. = 2.6 mg/kg/dose	Days 1 & 2	Dosing based on age at diagnosis	
Cyclophosphamide (CPM)	IV over 30 min	250 mg/m²/dose q12 hrs x 4 doses total	Days 3 & 4		
Mesna	IV over 30 min followed by CI	125 mg/m²/dose with CPM followed by 125 mg/m²/dose over 4 hrs (4 total doses/day)	Days 3 & 4	See Section 4.6.2 for infusion details	
Pegaspargase (PEG-ASP)	IM	2500 International units/m²/dose	Day 4 ONLY		
Dexamethasone (DEX)	PO/NG/IV	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) Dose < 1 MTX: 7.5mg HC: 7.5 mg ARAC: 15 mg ≥ 1 MTX: 8 mg HC: 8 mg ARAC: 16 mg	Days 1 & 15 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. on Day 5	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	

Therapy Delivery Map **Ht____cm** **Wt_____kg** **BSA_____m²**

Date Due	Date Given	Week	Day	VCR D1 &15 ___mg D8 ___@	DAUN ___mg	CPM ___mg ___mg	MESNA __mg __mg__mg __mg	PEG-ASP ____IU	DEX ___mg ___mg	ITT ___mg (MTX) ___mg (HC) ___mg (ARAC)	G-CSF ____mcg	Studies
				Enter calculated dose above and actual dose administered below								
		10	1	____mg	____mg				___mg ____mg	____mg (MTX) ____mg (HC) ____mg (ARAC)		a, b, c, d, e, f, g, h
			2		____mg				___mg ____mg			
			3			____mg ___mg	___mg ___mg___mg ___mg		___mg ____mg			
			4			____mg ___mg	___mg ___mg___mg ___mg	_____IU	___mg ____mg			
			5						___mg ____mg		____mcg	
			6						___mg ____mg			
			7						___mg ____mg			
		11	8	____mg@								
		12	15	_____mg					___mg ____mg	____mg (MTX) ____mg (HC) ____mg (ARAC)		b, e
			16						___mg ____mg			
			17						___mg ____mg			
			18						___mg ____mg			
			19						___mg ____mg			
			20						___mg ____mg			
			21						___mg ____mg			
			22	**Start next course (Consolidation, Section 4.6.3) on Day 22 or when blood count parameters are met (whichever occurs later).**								

Comments may be documented on a separate page. @ Dose differs on Day 8 Indicate last G-CSF if past Day 21_____

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.6.3 Consolidation: Weeks 13-19 (Arm B) ***(RETIRED)***

- To begin Consolidation, patient must have an ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.
- To begin Consolidation, patient must have recovered from mucositis and/or diaper area skin ulceration ≥ Grade 3.
- To begin Day 15 ETOP/CPM, patient must have ANC > 500/µL and platelets > 50,000/µL
- To begin Day 29 HD ARAC, patient must have an ANC > 500/µL and platelets > 50,000/µL and have been off G-CSF for at least 48 hours.

High Dose Methotrexate: IV
200 mg/m^2 IV over 20 minutes THEN 3800 mg/m^2 IV over remainder of 24 hours [4000 mg/m^2 IV in 24 hours] on Days 1 & 8. See Section 5.8 for IV fluid and dose modification guidelines.

Leucovorin rescue: Leucovorin will begin at T=42 hr at the standard dose of 15 mg/m^2/dose IV/PO q6 hours as long as the T=24 hr methotrexate level is < 150 µM, and will continue at this dose as long as the T=42 hr and T=48 hr methotrexate levels are < 1 µM and < 0.4 µM (all timed from the beginning of the methotrexate infusion), respectively. If any of the levels is above these thresholds, then the more detailed guidelines described in Section 5.8 will be followed.

HD MTX Infusion Guidelines:
See Appendix V for a flowchart of the HD MTX/LCV guidelines.

When IT therapy and HD MTX 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 HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM, as well as nonsteroidal anti-inflammatory agents, proton pump inhibitors, aspirin-containing drugs and penicillins.

Infants receiving therapeutic doses of amphotericin should have that drug withheld on the day HD MTX is administered and for the following 24 hours due to the risk of delayed MTX excretion, renal dysfunction and resultant toxicity.

See Appendix I for supportive care guidelines aimed at reducing the risk of perineal irritation associated with HD MTX administration.

Triple Intrathecal Chemotherapy: IT
Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)
Day 1 ONLY; deliver the IT therapy within 6 hrs of the beginning of the IV MTX infusion

Age-based dosing:	Age (years)	Dose
	< 1	MTX: 7.5 mg
		HC: 7.5 mg
		ARAC: 15 mg
	≥ 1	MTX: 8 mg
		HC: 8 mg
		ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Etoposide: IV over 2 hours
100 mg/m^2/dose on Days 15-19

Cyclophosphamide: IV over 30 minutes
300 mg/m^2/dose on Days 15-19

Mesna: IV
150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (2 total doses per day).

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 20 & Day 31, continuing until ANC > 1500/µL x 2 days post nadir.
Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

High Dose Cytarabine: IV over 3 hours
3000 mg/m^2/dose q12 hrs x 4 doses total on Days 29 and 30, beginning a min of 48 hrs AFTER G-CSF

Pegaspargase: IM
2500 International units/m^2/dose on Day 30 (3 hours after completion of final dose HD ARAC)

The therapy delivery map (TDM) for Consolidation is on the next page.

Following completion of Consolidation, the next course (Continuation I, Section 4.6.4) starts on Day 50 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later).

4.6.3.1 Consolidation (ARM B: IR/HR patients classified as MLL-R)

(RETIRED) Modified Consolidation is for IR/HR patients (7 weeks/49 days)

Patient name or initials _____ DOB _____

*Begin Consolidation when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 49 days and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High Dose Methotrexate (HD MTX)	IV	200 mg/m^2 over 20 min THEN 3800 mg/m^2 over remainder 24 hrs	Days 1 & 8	4000 mg/m^2 total in 24 hrs; see Section 5.8 for administration guidelines	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. MTX levels* d. Electrolytes/BUN Cr/AST/ALT/ T bili e. Serum IgG f. CSF cell count, diff, cytospin * MTX levels to be drawn per protocol with each dose of HD MTX **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	IV/PO	Start 15 mg/m^2/dose q6 hrs @ T=42 hr	Days 2 & 9	See Section 5.8 for administration guidelines	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg, HC: 7.5 mg, ARAC: 15 mg ≥ 1: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg	Day 1 ONLY	Deliver ITT within 6 hrs of beginning IV MTX infusion **Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 15-19	See below for criteria to begin ETOP/CPM	
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 15-19		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 15-19	See Section 4.6.3 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. on Days 20 & 31	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	3000 mg/m^2 q12 hrs x 4 doses total; begin min 48 hrs after G-CSF	Days 29 & 30	See below for criteria to begin HD ARAC; see Section 6.4 regarding administration of eye drops	
Pegaspargase (PEG-ASP)	IM	2500 International units/m^2/dose	Day 30	Admin 3 hrs after final HD ARAC	

Therapy Delivery Map **Ht____cm** **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Week	Day	HD MTX __mg __mg	LCV ___mg	ITT ___mg (MTX) ___mg (HC) ___mg (ARAC)	ETOP ___mg	CPM ____mg	MESNA ___mg ___mg	G-CSF ___mcg	HD ARAC __mg __mg	PEG-ASP ___IU	Studies
				Enter calculated dose above and actual dose administered below									
		13	1	__mg __mg		___mg (MTX) ___mg (HC) ___mg (ARAC)							a, b, c, d, e, f
			2		___mg								
			3-7		↓								
		14	8	__mg __mg									c
			9		___mg								
			10-14		↓								
		15	15*				___mg	___mg	___mg ___mg				b,d
			16				___mg	___mg	___mg ___mg				
			17				___mg	___mg	___mg ___mg				
			18				___mg	___mg	___mg ___mg				
			19				mg	mg	mg mg				
			20-21							___mcg			
		16	22-27							___mcg			
			28										
		17	29*								__mg __mg		b
			30								__mg __mg	___IU	
			31-35							___mcg			
		18	36-42							___mcg			
		19	43-49							___mcg			
			50	**Start next course (Continuation I, Section 4.6.4) on Day 50 or when blood count parameters are met (whichever occurs later).**									

Comments may be documented on a separate page. Indicate last G-CSF if past Day 49_____

* To begin Day 15 ETOP/CPM & Day 29 HD ARAC therapy, pt must have ANC > 500/µL & plts > 50,000/µL and been off G-CSF for at least 48 hrs

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.6.4 Continuation I: Weeks 20-49 (Arm B) ***(RETIRED)***

- To begin Continuation I, patient must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.
- For Weeks 21-23, 25-26, 34-36, 38-39 & 47-49 IV MTX/MP: Skip week if ANC < 500/µL or platelets < 50,000/µL.
- For Weeks 24 & 37: Begin regardless of counts 4 weeks after the start of Week 20/33.
- For Weeks 27 & 40: Begin when ANC > 750/µL and platelets > 75,000/µL.
- For Weeks 30 & 43: Begin when off G-CSF for at least 48 hours and ANC > 750/µL and platelets > 75,000/µL.
- For Weeks 33 & 46: Begin regardless of counts once off G-CSF for at least 48 hours.

CYCLE #1: (Weeks 20-23)

Week 20 **VinCRIStine:** 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY

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."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5

Triple Intrathecal Therapy: Day 1 ONLY [Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)]

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Weeks 21-23 **Methotrexate:** 20 mg/m^2/dose IV push weekly (Day 1 of each week)

Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

CYCLE #2: (Weeks 24-32)

Week 24 **VinCRIStine:** 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY

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."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate

liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5
Triple Intrathecal Therapy: Day 1 ONLY [Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)]

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Weeks 25-26 **Methotrexate:** 20 mg/m^2/dose IV push weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Weeks 27-29 **Etoposide:** 100 mg/m^2/dose IV over 2 hours Days 1-5 of Week 27 ONLY
Cyclophosphamide: 300 mg/m^2/dose IV over 30 minutes Days 1-5 of Week 27 ONLY
Mesna: 150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (2 total doses per day)
Filgrastim: 5 mcg/kg/dose SubQ daily beginning Day 6 of Week 27, until ANC > 1500/µL x 2 days post nadir. Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

Weeks 30-32 **High Dose Cytarabine:** 3000 mg/m^2/dose IV over 3 hours q12 hours x 4 doses total Days 1-2 of Week 30 ONLY
Pegaspargase: 2500 International units/m^2/dose IM Day 2 (3 hrs after completion of final HD ARAC) of Week 30 ONLY
Filgrastim: 5 mcg/kg/dose SubQ daily beginning Day 3 of Week 30, until ANC > 1500/µL x 2 days post nadir. Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

CYCLE #3: (Weeks 33-36) Repeat Cycle #1

CYCLE #4: (Weeks 37-45) Repeat Cycle #2

CYCLE #5: (Weeks 46-49) Repeat Cycle #1

The therapy delivery maps (TDMs) for Continuation I are on the next three (3) pages.

Following completion of Continuation I, the next course (Continuation II, Section 4.6.5) starts the day after Week 49/Day 28 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later).

4.6.4.1 **Continuation I (ARM B: IR/HR patients classified as MLL-R)** ***(RETIRED)***

Modified Continuation I is for IR/HR patients (30 weeks/210 days). Continuation I occurs in five cycles. Cycle #1 lasts 4 weeks, includes the therapy described below and is repeated during Cycles #3 and #5. [*Cycle #2 lasts 9 weeks, includes the therapy described on pages 2-3 and is repeated during Cycle #4*]

_____
Patient name or initials

_____
DOB

Begin Continuation I when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 210 days and this Therapy Delivery Map is on ***three (3)*** *pages. Cycles 1, 3 and 5 are described below.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push	0.05 mg/kg/dose	Day 1 ONLY	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN/Cr/AST/ALT/ T bili d. Serum IgG e. CrCl or GFR f. CSF cell count, diff, cytospin g. Local BM eval h. *OPTIONAL BM for flow MRD, molec. MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m^2/dose BID	Days 1-5	Total daily dose: 6 mg/m^2/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) Dose < 1 MTX: 7.5mg HC: 7.5 mg ARAC: 15 mg ≥ 1 MTX: 8 mg HC: 8 mg ARAC: 16 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (IV MTX)	IV push	20 mg/m^2/dose	Days 8, 15 & 22		
Mercaptopurine (MP)	PO/NG	75 mg/m^2/dose	Days 8-28	Should be given on an empty stomach	

Circle Cycle #: 1 3 5 **Ht____cm** **Wt____kg** **BSA____m^2**

Date Due	Date Given	Week	Day	VCR ____mg	DEX ___mg ___mg	ITT ____mg (MTX) ____mg (HC) ____mg (ARAC)	IV MTX ____mg	MP ____mg	Studies
				Enter calculated dose above and actual dose administered below					
		20/33[α]/46[α]	1	____mg	___mg ___mg	____mg (MTX) ____mg (HC) ____mg (ARAC)			a*, b, d, f, (c, e, g, h)*
			2		___mg ___mg				
			3		___mg ___mg				
			4		___mg ___mg				
			5		___mg ___mg				
			6-7						
		(21/34/47)[β]	8				____mg	____mg	b
			9						
			10						
			11						
			12						
			13						
			14						
		(22/35/48)[β]	15				____mg		b
			16						
			17						
			18						
			19						
			20						
			21						
		(23/36/49)[β]	22				____mg		b
			23						
			24						
			25						
			26						
			27						
			28						
			29	**Start next course (Continuation II, Section 4.6.5) the day after Week 49/Day 28 or when blood count parameters are met (whichever occurs later).**					

Comments may be documented on a separate page.

* Cycle #1 (Week 20) ONLY

[α] Begin regardless of counts once off G-CSF for at least 48 hrs

[β] For IV MTX/MP: skip week if ANC < 500/µL or plts < 50,000/µL

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.6.4.1 Continuation I (ARM B: IR/HR patients classified as MLL-R) *(RETIRED)*

Modified Continuation I is for IR/HR patients (30 weeks/210 days). Continuation I occurs in five cycles. Cycle #2 lasts 9 weeks, includes the therapy described below and is repeated during Cycle #4. [*Cycle #1 lasts 4 weeks, includes the therapy described previously and is repeated during Cycles #3 and #5*]

_____
Patient name or initials

_____
DOB

*Begin Continuation I when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 210 days and this Therapy Delivery Map is on **three (3)** pages. Cycles 2 and 4 are described below.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg/dose	Day 1 ONLY	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/ASTALT/T bili d. Serum IgG e. CrCl or GFR f. CSF cell count, diff, cytospin g. Local BM eval h. *OPTIONAL BM for flow MRD, molec. MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m^2/dose BID	Days 1-5	Total daily dose: 6 mg/m^2/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) Dose < 1 MTX: 7.5mg HC: 7.5 mg ARAC: 15 mg ≥ 1 MTX: 8 mg HC: 8 mg ARAC: 16 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (IV MTX)	IV push	20 mg/m^2/dose	Days 8 & 15		
Mercaptopurine (MP)	PO/NG	75 mg/m^2/dose	Days 8-21	Should be given on an empty stomach	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 22-26	See below for criteria to begin ETOP/CPM	
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 22-26		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 22-26	See Section 4.6.4 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Days 27 & 45	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	3000 mg/m^2/dose q12 hrs x 4 doses total; begin min 48 hrs after G-CSF	Days 43 & 44	See below for criteria to begin HD ARAC; see Section 6.4 regarding administration of eye drops	
Pegaspargase (PEG-ASP)	IM	2500 International units/m^2/dose	Day 44	3 hrs after final HD ARAC	

Circle Cycle #: 2 4 **Ht ___cm** **Wt ___kg** **BSA ___m^2**

Date Due	Date Given	Week	Day	VCR ___mg	DEX __mg __mg	ITT __mg (MTX) __mg (HC) __mg (ARAC)	IV MTX ___mg	MP ____mg	ETOP ____mg	CPM ____mg	MESNA ___mg ___mg	G-CSF ____mcg	Studies
				Enter calculated dose above and actual dose administered below									
		(24/37)α	1	___mg	__mg __mg	__mg (MTX) __mg (HC) __mg (ARAC)							b, d, f
			2		__mg __mg								
			3		__mg __mg								
			4		__mg __mg								
			5		__mg __mg								
			6-7										
		(25/38)β	8				___mg	____mg					b
			9-14										
		(26/39)β	15				___mg						b
			16-20										
			21										c, d
		(27/40)γ	22						___mg	___mg	___mg ___mg		b
			23						___mg	___mg	___mg ___mg		
			24						___mg	___mg	___mg ___mg		
			25						___mg	___mg	___mg ___mg		
			26						___mg	___mg	___mg ___mg		
			27									____mcg	

Comments may be documented on a separate page.

α Begin regardless of counts 4 weeks after start of Week 20/33

β For IV MTX/MP: skip week if ANC < 500/µL or platelets < 50,000/µL

γ Begin when ANC > 750/µL & platelets > 75,000/µL

4.6.4.1 **Continuation I (ARM B: IR/HR patients classified as MLL-R)** ***(RETIRED)***

Modified Continuation I is for IR/HR patients (30 weeks/210 days). Continuation I occurs in five cycles. Cycle #2 lasts 9 weeks, includes the therapy described below and is repeated during Cycle #4. [*Cycle #1 lasts 4 weeks, includes the therapy described previously and is repeated during Cycles #3 and #5*]

Patient name or initials

DOB

Begin Continuation I when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 210 days and this Therapy Delivery Map is on ***three (3)*** *pages. Cycles 2 and 4 are described below.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg/dose	Day 1 ONLY	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/T bili d. Serum IgG e. CrCl or GFR f. CSF cell count, diff, cytospin g. Local BM eval h. *OPTIONAL BM for flow & molec. MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m²/dose BID	Days 1-5	Total daily dose: 6 mg/m²/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg, HC: 7.5 mg, ARAC: 15 mg ≥ 1: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (IV MTX)	IV push	20 mg/m²/dose	Days 8 & 15		
Mercaptopurine (MP)	PO/NG	75 mg/m²/dose	Days 8-21	Should be given on an empty stomach	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m²/dose	Days 22-26	See below for criteria to begin ETOP/CPM	
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m²/dose	Days 22-26		
Mesna	IV over 30 min followed by CI	150 mg/m²/dose with CPM followed by 150 mg/m²/dose over 4 hrs daily (2 total doses/day)	Days 22-26	See Section 4.6.4 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Days 27 & 45	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	3000 mg/m²/dose q12 hrs x 4 doses total; begin min 48 hrs after G-CSF	Days 43 & 44	See below for criteria to begin HD ARAC; see Section 6.4 regarding administration of eye drops	
Pegaspargase (PEG-ASP)	IM	2500 International units/m²/dose	Day 44	3 hrs after final HD ARAC	

Circle Cycle #: 2 4 **Ht____cm** **Wt____kg** **BSA____m²**

Date Due	Date Given	Week	Day	HD ARAC ____mg ____mg	PEG-ASP ____IU	G-CSF ____mcg	Studies
				Enter calculated dose above and actual dose administered below			
		28/41	29-35			____mcg	b
		29/42	36-41			____mcg	b
			42				
		(30/43)α	43	____mg ____mg			a, b, d
			44	____mg ____mg	____IU		
			45-49			____mcg	
		31/44	50-56			____mcg	b
		32/45	57-63			____mcg	b

Indicate last G-CSF if past Day 63 _____

Comments may be documented on a separate page.

α Begin when ANC > 750/µL & plts > 75,000/µL and been off G-CSF for at least 48 hrs

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.6.5 Continuation II: Weeks 50-104 (Arm B) ***(RETIRED)***

To begin Continuation II, patients must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.

Each cycle of Continuation II lasts 12 weeks and should be repeated until 2 calendar years from diagnosis.

Week 50

VinCRIStine: 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5
IT Methotrexate: < 1 year: 7.5 mg Day 1 ONLY
1 year - < 2 years: 8 mg Day 1 ONLY
≥ 2 years: 10 mg Day 1 ONLY
See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Weeks 51-53

Methotrexate: 20 mg/m^2/dose PO/NG weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph).

Week 54

VinCRIStine: 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2 PO/NG/IV divided BID Days 1-5

Weeks 55-57

Methotrexate: 20 mg/m^2/dose PO/NG weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph).

Continue repeating 12week cycles until 2 years from diagnosis (see below for remaining cycle information)

Week 58	**VinCRIStine:** 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY 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." Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable. **Dexamethasone:** 6 mg/m^2/day PO/NG/IV divided BID Days 1-5	Continue repeating 12 week cycles until 2 years from diagnosis (see above for Week 50-57)
Weeks 59-61	**Methotrexate:** 20 mg/m^2/dose PO/NG weekly (Day 1 of each week) **Mercaptopurine:** 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph).	

The therapy delivery map (TDM) for Continuation II is on the next page.

4.6.5.1 **Continuation II (ARM B: IR/HR patients classified as MLL-R)**

(RETIRED) Modified Continuation II is for IR/HR patients (12 week cycles repeated until 2 years from diagnosis). Each cycle is 12 weeks in length and includes the therapy described below.

Patient name or initials

DOB

Begin Continuation II when ANC > 750/μL and platelets > 75,000/μL and have been off G-CSF for at least 48 hrs. This Course is composed of 12-week cycles that are repeated until 2 calendar years from diagnosis; this Therapy Delivery Map describes one cycle and is on ***one (1)*** *page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	0.05 mg/kg/dose	Days 1, 29, 57	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN/Cr/AST/ ALT/T bili d. Serum IgG e. CSF cell count, diff, cytospin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m^2/dose BID	Days 1-5, 29-33, 57-61	Total daily dose: 6 mg/m^2/day, divided BID	
Intrathecal Methotrexate (IT MTX)	IT	Age (years) Dose < 1 7.5 mg 1 - < 2 8 mg ≥ 2 10 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (MTX)	PO/NG	20 mg/m^2/dose	Days 8, 15, 22, 36, 43, 50, 64, 71, 78	Hold with IT MTX	
Mercaptopurine (MP)	PO/NG	75 mg/m^2/dose	Days 8-28, 36-56, 64-84	Should be given on an empty stomach	

Cycle # _____ Ht _____ cm Wt _____ kg BSA _____ m^2

Date Due	Date Given	Week	Day	VCR ___ mg	DEX ___ mg ___ mg	IT MTX ___ mg	PO MTX ___ mg	MP ___ mg	Studies
				Enter calculated dose above and actual dose administered below					
		50	1	___mg	___mg ___mg	___mg			(a, c, d, e)*, b
			2-5		___mg ___mg				
			6-7						
		51	8				___mg	___mg	
			9-14						
		52	15				___mg		
			16-21						
		53	22				___mg		
			23-28						
		54	29	___mg	___mg ___mg				b
			30-33		___mg ___mg				
			34-35						
		55	36				___mg	___mg	
			37-42						
		56	43				___mg		
			44-49						
		57	50				___mg		
			51-56						
		58	57	___mg	___mg ___mg				b
			58-61		___mg ___mg				
			62-63						
		59	64				___mg	___mg	
			65-70						
		60	71				___mg		
			72-77						
		61	78				___mg		
			79-84						
			End of Therapy						

Comments may be documented on a separate page.

***** Start of each 12-week cycle

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.7 Post-Induction Arm C [Chemotherapy + Lestaurtinib for IR /HR Patients (MLL-R)]

Note: Post-Induction Arm C therapy is limited to IR/HR patients enrolled at COG sites in the US and Canada (see Section 3.1.7).

To avoid diaper area skin ulceration, especially at Weeks 6 and 7 of HD MTX, please see **Appendix I**, section on Perineal Irritation.

4.7.1 Induction Intensification: Weeks 6-9 (Arm C)

- Begin Induction Intensification when ANC > 750/µL and platelets > 75,000/µL and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less.
- To begin Day 8 HD MTX, mucositis or diaper area skin ulceration ≥ Grade 3 must have improved to Grade 2 or less.

High Dose Methotrexate: IV
200 mg/m^2 IV over 20 minutes THEN 3800 mg/m^2 IV over remainder of 24 hours [4000 mg/m^2 IV in 24 hours] on Days 1 & 8. See Section 5.8 for IV fluid and dose modification guidelines.

Leucovorin rescue: Leucovorin will begin at T=42 hr at the standard dose of 15 mg/m^2/dose IV/PO q6 hours as long as the T=24 hr methotrexate level is < 150 µM, and will continue at this dose as long as the T=42 hr and T=48 hr methotrexate levels are < 1 µM and < 0.4 µM (all timed from the beginning of the methotrexate infusion), respectively. If any of the levels is above these thresholds, then the more detailed guidelines described in Section 5.8 will be followed.

HD MTX Infusion Guidelines:
See Appendix V for a flowchart of the HD MTX/LCV guidelines.

When IT therapy and HD MTX 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 HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM, as well as nonsteroidal anti-inflammatory agents, proton pump inhibitors, aspirin-containing drugs and penicillins.

Infants receiving therapeutic doses of amphotericin should have that drug withheld on the day HD MTX is administered and for the following 24 hours due to the risk of delayed MTX excretion, renal dysfunction and resultant toxicity.

See Appendix I for supportive care guidelines aimed at reducing the risk of perineal irritation associated with HD MTX administration.

Triple Intrathecal Chemotherapy: IT
Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)
Days 1 & 8; deliver the IT therapy within 6 hrs of the beginning of the IV MTX infusion

Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg HC: 7.5 mg ARAC: 15 mg
≥ 1	MTX: 8 mg HC: 8 mg ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Etoposide: IV over 2 hours
100 mg/m^2/dose on Days 15-19

Cyclophosphamide: IV over 30 minutes
300 mg/m^2/dose on Days 15-19

Mesna: IV
150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion (CI) IV over 4 hours following each dose of cyclophosphamide (2 total doses per day).

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 20 and until ANC > 1500/µL x 2 days post nadir.
Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

Lestaurtinib: PO/NG
Intermediate Risk patients: 5 mg/kg/day (with food) divided BID on Days 20-27

High Risk patients: 4.25 mg/kg/day (with food) divided BID on Days 20-27

Please see Appendices II and III regarding contraindicated medications during lestaurtinib administration.

Lestaurtinib is diluted in juice prior to administration. Dilution instructions are available in the drug monograph (Section 6.10) and Appendix IV.

The therapy delivery map (TDM) for Induction Intensification is on the next page.

Following completion of Induction Intensification, the next course (Re-Induction, Section 4.7.2) starts on Day 29 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later). Patients must also be in morphologic remission in order to begin Re-Induction.

4.7.1.1 Induction Intensification (ARM C: IR/HR patients classified as MLL-R)

Modified Induction Intensification + Lestaurtinib is for IR/HR patients (4 weeks/28 days)

Patient name or initials _____ DOB _____

*Begin Induction Intensification when ANC > 750/µL and platelets > 75,000/µL and mucositis/diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less. This Course lasts 28 days and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High Dose Methotrexate (HD MTX)	IV	200 mg/m^2 over 20 min THEN 3800 mg/m^2 over remainder 24 hrs	Days 1 & 8*	4000 mg/m^2 total in 24 hrs; see Section 4.7.1 for administration guidelines	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/T bili d. Serum IgG e. CSF cell count, diff, cytospin f. Local BM eval g. PB for Lestaurtinib PK/PIA (see Section 13.1 for details) h. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	IV/PO	Start 15 mg/m^2/dose q6 hrs @ T=42 hr	Days 2 & 9	See Section 4.7.1 for administration guidelines	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg, HC: 7.5 mg, ARAC: 15 mg ≥ 1: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg	Days 1 & 8	Deliver ITT within 6 hrs of beginning IV MTX infusion **Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 15-19		
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 15-19		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 15-19	See Section 4.7.1 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. on Day 20	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
Lestaurtinib (LEST)	PO/NG	IR: 5 mg/kg/day divided BID HR: 4.25 mg/kg/day divided BID	Days 20-27	Should be given with food	

Therapy Delivery Map **Ht____cm** **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Week	Day	HD MTX __mg __mg	LCV ____mg	ITT ___mg (MTX) ___mg (HC) ___mg (ARAC)	ETOP ____mg	CPM ____mg	MESNA ___mg ___mg	G-CSF ____mcg	LEST ____mg ____mg	Studies
				Enter calculated dose above and actual dose administered below								
		6	1	__mg __mg		___mg (MTX) ___mg (HC) ___mg (ARAC)						a, b, c, d, e, f, h
			2		____mg							
			3-7		↓							
		7	8*	__mg __mg *		___mg (MTX) ___mg (HC) ___mg (ARAC)						b, e
			9		____mg							
			10-14		↓							
		8	15				____mg	____mg	___mg ___mg			b, d
			16				____mg	____mg	___mg ___mg			
			17				____mg	____mg	___mg ___mg			
			18				____mg	____mg	___mg ___mg			
			19				____mg	____mg	___mg ___mg			
			20							____mcg	____mg ____mg	g
			21							↓	____mg ____mg	
		9	22								____mg ____mg	
			23								____mg ____mg	
			24								____mg ____mg	
			25								____mg ____mg	
			26								____mg ____mg	
			27								____mg ____mg	g
			28									
			29	**Start next course (Re-Induction, Section 4.7.2) on Day 29 or when blood count parameters are met (whichever occurs later).**								

Comments may be documented on a separate page. Indicate last G-CSF if past Day 28 _____

* To receive Day 8 HD MTX, mucositis or diaper area skin ulceration ≥ Grade 3 must have improved to Grade 2 or less

4.7.2 Re-Induction: Weeks 10-12 (Arm C)

To begin Re-Induction, patients must be in morphologic remission to proceed with therapy. Patient must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF at least 48 hours.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
0.05 mg/kg on Days 1 & 15 AND 0.03 mg/kg on Day 8

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."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

DAUNOrubicin: IV over 30 minutes
Days 1 & 2

Dose is mg/kg/day based on age at diagnosis:
< 6 months = 1.7 mg/kg/dose
6 months to 8.99 months = 2.1 mg/kg/dose
≥ 9 months = 2.6 mg/kg/dose

Cyclophosphamide: IV over 30 minutes
250 mg/m^2/dose q12 hours x 4 doses total on Days 3 & 4

Mesna: IV
125 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 125 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (4 total doses per day).

Pegaspargase: IM
2500 International units/m^2/dose on Day 4

Dexamethasone: PO/NG/IV
10 mg/m^2/day divided BID on Days 1-7 & 15-21

Triple Intrathecal Chemotherapy: IT
Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)
Days 1 & 15 ONLY

Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 5 and until ANC > 1500/µL x 2 days post nadir
Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

Lestaurtinib: PO/NG
Intermediate Risk patients: 5 mg/kg/day (with food) divided BID on Days 5-20

High Risk patients: 4.25 mg/kg/day (with food) divided BID on Days 5-20

Please see Appendices II and III regarding contraindicated medications during lestaurtinib administration.

Lestaurtinib is diluted in juice prior to administration. Dilution instructions are available in the drug monograph (Section 6.10) and Appendix IV.

The therapy delivery map (TDM) for Re-Induction is on the next page.

Following completion of Re-Induction, the next course (Consolidation, Section 4.7.3) starts on Day 22 or when counts recover, G-CSF has been discontinued for at least 48 hours and mucositis and/or diaper area skin ulceration ≥ Grade 3 has improved to Grade 2 or less (whichever occurs later).

4.7.2.1 Re-Induction (ARM C: IR/HR patients classified as MLL-R)

Modified Re-Induction + Lestaurtinib is for IR/HR patients (3 weeks/21 days)

_____ Patient name or initials _____ DOB

*Begin Re-Induction if patient is in morphologic remission; patient must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 21 days and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg on Days 1 & 15 AND 0.03 mg/kg on Day 8@	Days 1, 8@, 15	+ Or infusion via minibag as per institutional policy @ Dose differs on Day 8	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/T bili d. Serum IgG e. CSF cell count, cytospin f. Echo or MUGA g. Local BM eval h. PB for Lestaurtinib PK/PIA (see Section 13.1 for details) i. *OPTIONAL BM for flow MRD, molecular MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
DAUNOrubicin (DAUN)	IV over 30 min	Age at diagnosis: < 6 mos. = 1.7 mg/kg/dose 6-8.99 mos.= 2.1 mg/kg/dose ≥ 9 mos. = 2.6 mg/kg/dose	Days 1 & 2	Dosing based on age at diagnosis	
Cyclophosphamide (CPM)	IV over 30 min	250 mg/m²/dose q12 hrs x 4 doses total	Days 3 & 4		
Mesna	IV over 30 min followed by CI	125 mg/m²/dose with CPM followed by 125 mg/m²/dose over 4 hrs (4 total doses/day)	Days 3 & 4	See Section 4.7.2 for infusion details	
Pegaspargase (PEG-ASP)	IM	2500 International units/m²/dose	Day 4 ONLY		
Dexamethasone (DEX)	PO/NG/IV	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg; HC: 7.5 mg; ARAC: 15 mg ≥ 1: MTX: 8 mg; HC: 8 mg; ARAC: 16 mg	Days 1 & 15 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Day 5	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
Lestaurtinib (LEST)	PO/NG	IR: 5 mg/kg/day divided BID HR: 4.25 mg/kg/day divided BID	Days 5-20	Should be given with food	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA_____m²**

Date Due	Date Given	Week	Day	VCR D1 & 15 ___mg D8 ____@	DAUN ___mg	CPM ___mg ___mg	MESNA ___mg ___mg	PEG-ASP ___IU	DEX __mg __mg	ITT __mg (MTX) __mg (HC) __mg (ARAC)	LEST __mg __mg	G-CSF ___mcg	Studies
				Enter calculated dose above and actual dose administered below									
		10	1	___mg	___mg				__mg __mg	__mg (MTX) __mg (HC) __mg (ARAC)			a, b, c, d, e, f, g, i
			2		___mg				__mg __mg				
			3			___mg ___mg	___mg ___mg ___mg ___mg		__mg __mg				
			4			___mg ___mg	___mg ___mg ___mg ___mg	___IU	__mg __mg				
			5-7						__mg __mg		__mg __mg	___mcg	
		11	8	___mg@									
			9										
			10-11										
			12										
			13-14										
		12	15	___mg					__mg __mg	__mg (MTX) __mg (HC) __mg (ARAC)			b, e
			16-18						__mg __mg				
			19						__mg __mg				h
			20						__mg __mg				
			21						__mg __mg				
			22	**Start next course (Consolidation, Section 4.7.3) on Day 22 or when blood count parameters are met (whichever occurs later).**									

Comments may be documented on a separate page. @ Dose differs on Day 8 Indicate last G-CSF if past Day 21 _____

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.7.3 Consolidation: Weeks 13-19 (Arm C)

- To begin Consolidation, patient must have an ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.
- To begin Consolidation, patient must have recovered from mucositis and/or diaper area skin ulceration ≥ Grade 3.
- To begin Day 15 ETOP/CPM, patient must have ANC > 500/µL and platelets > 50,000/µL
- To begin Day 29 HD ARAC, patient must have an ANC > 500/µL and platelets > 50,000/µL and have been off G-CSF for at least 48 hours.

High Dose Methotrexate: IV
200 mg/m^2 IV over 20 minutes THEN 3800 mg/m^2 IV over remainder of 24 hours [4000 mg/m^2 IV in 24 hours] on Days 1 & 8. See Section 5.8 for IV fluid and dose modification guidelines.

Leucovorin rescue: Leucovorin will begin at T=42 hr at the standard dose of 15 mg/m^2/dose IV/PO q6 hours as long as the T=24 hr methotrexate level is < 150 µM, and will continue at this dose as long as the T=42 hr and T=48 hr methotrexate levels are < 1 µM and < 0.4 µM (all timed from the beginning of the methotrexate infusion), respectively. If any of the levels is above these thresholds, then the more detailed guidelines described in Section 5.8 will be followed.

HD MTX Infusion Guidelines:
See Appendix V for a flowchart of the HD MTX/LCV guidelines.

When IT therapy and HD MTX 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 HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM, as well as nonsteroidal anti-inflammatory agents, proton pump inhibitors, aspirin-containing drugs and penicillins.

Infants receiving therapeutic doses of amphotericin should have that drug withheld on the day HD MTX is administered and for the following 24 hours due to the risk of delayed MTX excretion, renal dysfunction and resultant toxicity.

See Appendix I for supportive care guidelines aimed at reducing the risk of perineal irritation associated with HD MTX administration.

Triple Intrathecal Chemotherapy: IT
Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)
Day 1 ONLY; deliver the IT therapy within 6 hrs of the beginning of the IV MTX infusion.

Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Etoposide: IV over 2 hours
100 mg/m^2/dose on Days 15-19

Cyclophosphamide: IV over 30 minutes
300 mg/m^2/dose on Days 15-19

Mesna: IV
150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (2 total doses per day).

Filgrastim: SubQ/IV
5 mcg/kg daily/dose beginning on Day 20 & Day 31, continuing until ANC > 1500/µL x 2 days post nadir. Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

High Dose Cytarabine: IV over 3 hours
3000 mg/m^2/dose q12 hrs x 4 doses total on Days 29 & 30, beginning a minimum of 48 hrs AFTER G-CSF

Pegaspargase: IM
2500 International units/m^2/dose on Day 30 (3 hrs after completion of final dose HD ARAC)

Lestaurtinib: PO/NG
Intermediate Risk patients: 5 mg/kg/day (with food) divided BID on Days 20-27 and 31-42

High Risk patients: 4.25 mg/kg/day (with food) divided BID on Days 20-27 and 31-42

Please see Appendices II and III regarding contraindicated medications during lestaurtinib administration.

Lestaurtinib is diluted in juice prior to administration. Dilution instructions are available in the drug monograph (Section 6.10) and Appendix IV.

The therapy delivery map (TDM) for Consolidation is on the next page.

Following completion of Consolidation, the next course (Continuation I, Section 4.7.4) starts on Day 50 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later).

4.7.3.1 Consolidation (ARM C: IR/HR patients classified as MLL-R)

Modified Consolidation + Lestaurtinib is for IR/HR patients (7 weeks/49 days)

Patient name or initials _____ DOB _____

*Begin Consolidation when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 49 days and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High Dose Methotrexate (HD MTX)	IV	200 mg/m^2 over 20 min THEN 3800 mg/m^2 over remainder 24 hrs	Days 1 & 8	4000 mg/m^2 total in 24 hrs; see Section 4.7.3 for administration guidelines	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. MTX levels* d. Electrolytes/ BUN/Cr/AST/ ALT/T bili e. Serum IgG f. CSF cell count, diff, cytospin * MTX levels to be drawn per protocol with each dose of HD MTX **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	IV/PO	Start 15 mg/m^2/dose q6 hrs @ T=42 hrs	Days 2 & 9	See Section 4.7.3 for administration guidelines	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg, HC: 7.5 mg, ARAC: 15 mg ≥ 1: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg	Day 1 ONLY	Deliver ITT within 6 hrs of beginning IV MTX infusion **Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose	Days 15-19	See below for criteria to begin ETOP/CPM	
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m^2/dose	Days 15-19		
Mesna	IV over 30 min followed by CI	150 mg/m^2/dose with CPM followed by 150 mg/m^2/dose over 4 hrs daily (2 total doses/day)	Days 15-19	See Section 4.7.3 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Days 20 & 31	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	3000 mg/m^2/dose q12 hrs x 4 doses total; begin min 48 hrs after G-CSF	Days 29 & 30	See below for criteria to begin HD ARAC; see Section 6.4 regarding administration of eye drops	
Pegaspargase (PEG-ASP)	IM	2500 International units/m^2/dose	Day 30	3 hrs after final HD ARAC	
Lestaurtinib (LEST)	PO/NG	IR: 5 mg/kg/day divided BID HR: 4.25 mg/kg/day divided BID	Days 20-27 & 31-42	Should be given with food	

Therapy Delivery Map **Ht____cm** **Wt____kg** **BSA____m^2**

Date Due	Date Given	Week	Day	HD MTX __mg __mg	LCV ___mg	ITT ___mg (MTX) ___mg (HC) ___mg (ARAC)	ETOP ____mg	CPM ____mg	MESNA __mg __mg	G-CSF ___mcg	HD ARAC __mg __mg	PEG-ASP ___IU	LEST __mg __mg	Studies
				Enter calculated dose above and actual dose administered below										
			1	__mg __mg		___mg (MTX) ___mg (HC) ___mg (ARAC)								a, b, c, d, e, f
			2		___mg									
			3-7		↓									
		14	8	__mg __mg										c
			9		___mg									
			10-14		↓									
		15	15**				____mg	____mg	__mg __mg					b, d
			16				____mg	____mg	__mg __mg					
			17				____mg	____mg	__mg __mg					
			18				____mg	____mg	__mg __mg					
			19				____mg	____mg	__mg __mg					
			20-21							___mcg			__mg __mg	
		16	22-27							___mcg			__mg __mg	
			28											
		17	29**								__mg __mg			b
			30								__mg __mg	___IU		
			31-35							___mcg			__mg __mg	
		18	36-42							___mcg			__mg __mg	
		19	43-49							___mcg				
			50	**Start next course (Continuation I, Section 4.7.4) on Day 50 or when blood count parameters are met (whichever occurs later).**										

Comments may be documented on a separate page. Indicate last G-CSF if past Day 49 _____

** To begin Day 15 ETOP/CPM & Day 29 HDARAC therapy, pt must have ANC > 500/µL & plts > 50,000/µL and been off G-CSF for at least 48 hrs

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.7.4 Continuation I: Weeks 20-49 (Arm C)

- To begin Continuation I, patients must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.
- For Weeks 21-23, 25-26, 34-36, 38-39 & 47-49 IV MTX/MP: Skip week if ANC < 500/µL or platelets < 50,000/µL.
- For Weeks 24 & 37: Begin regardless of counts 4 weeks after the start of Week 20/33.
- For Weeks 27 & 40: Begin when ANC > 750/µL and platelets > 75,000/µL.
- For Weeks 30 & 43: Begin when off G-CSF for at least 48 hours and ANC > 750/µL and platelets > 75,000/µL.
- For Weeks 33 & 46: Begin regardless of counts once off G-CSF for at least 48 hours.

CYCLE #1: (Weeks 20-23)

Week 20 **VinCRIStine:** 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY

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."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5

Triple Intrathecal Therapy: Day 1 ONLY [Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)]

Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Lestaurtinib: for Intermediate Risk patients, 5 mg/kg/day, and for High Risk patients, 4.25 mg/kg/day (with food) PO/NG divided BID Days 2-6

Weeks 21-23 **Methotrexate:** 20 mg/m^2/dose IV push weekly (Day 1 of each week)

Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

CYCLE #2: (Weeks 24-32)

Week 24 **VinCRIStine:** 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY

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."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5
Triple Intrathecal Therapy: Day 1 ONLY [Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)]
Age-based dosing:

Age (years)	Dose
< 1	MTX: 7.5 mg
	HC: 7.5 mg
	ARAC: 15 mg
≥ 1	MTX: 8 mg
	HC: 8 mg
	ARAC: 16 mg

See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration
Lestaurtinib: for Intermediate Risk patients, 5 mg/kg/day, and for High Risk patients, 4.25 mg/kg/day (with food) PO/NG divided BID Days 2-6

Weeks 25-26 **Methotrexate:** 20 mg/m^2/dose IV push weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Weeks 27-29 **Etoposide:** 100 mg/m^2/dose IV over 2 hours Days 1-5 of Week 27 ONLY
Cyclophosphamide: 300 mg/m^2/dose IV over 30 minutes Days 1-5 of Week 27 ONLY
Mesna: 150 mg/m^2/dose infused with each dose of cyclophosphamide over 30 minutes; then 150 mg/m^2/dose continuous infusion IV over 4 hours following each dose of cyclophosphamide (2 total doses per day).
Filgrastim: 5 mcg/kg/dose SubQ daily beginning Day 6 of Week 27, until ANC > 1500/µL x 2 days post nadir. Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.
Lestaurtinib: for Intermediate Risk patients, 5 mg/kg/day, and for High Risk patients, 4.25 mg/kg/day (with food) PO/NG divided BID Days 27-41

Weeks 30-32 **High Dose Cytarabine:** 3000 mg/m^2/dose IV over 3 hours q12 hours x 4 doses total Days 1-2 of Week 30 ONLY
Pegaspargase: 2500 International units/m^2/dose IM Day 2 (3 hrs after completion of final HD ARAC) of Week 30 ONLY
Filgrastim: 5 mcg/kg/dose SubQ daily beginning Day 3 of Week 30, until ANC > 1500/µL x 2 days post nadir. Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.
Lestaurtinib: for Intermediate Risk patients, 5 mg/kg/day, and for High Risk patients, 4.25 mg/kg/day (with food) PO/NG divided BID Days 45-56

CYCLE #3: (Weeks 33-36) Repeat Cycle #1

CYCLE #4: (Weeks 37-45) Repeat Cycle #2

CYCLE #5: (Weeks 46-49) Repeat Cycle #1

Dosing for lestaurtinib: for Intermediate Risk patients, 5 mg/kg/day, and for High Risk patients, 4.25 mg/kg/day:

Please see Appendices II and III regarding contraindicated medications during lestaurtinib administration.

Lestaurtinib is diluted in juice prior to administration. Dilution instructions are available in the drug monograph (Section 6.10) and Appendix IV.

The therapy delivery maps (TDMs) for Continuation I are on the next three (3) pages.

Following completion of Continuation I, the next course (Continuation II, Section 4.7.5) starts the day after Week 49/Day 28 or when counts recover and G-CSF has been discontinued for at least 48 hours (whichever occurs later).

4.7.4.1 **Continuation I (ARM C: IR/HR patients classified as MLL-R)** Modified Continuation I + Lestaurtinib is for IR/HR patients (30 weeks/210 days). Continuation I occurs in five cycles. Cycle #1 lasts 4 weeks, includes the therapy described below and is repeated during Cycles #3 and #5. [*Cycle #2 lasts 9 weeks, includes the therapy described on pages 2-3 and is repeated during Cycle #4*]	_____ Patient name or initials _____ DOB

*Begin Continuation I when ANC > 750/μL and platelets > 75,000/μL and have been off G-CSF for at least 48 hrs. This Course lasts 30 weeks (Weeks 20-49) and this Therapy Delivery Map is on **three (3)** pages. Cycles 1, 3 and 5 are described below.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	0.05 mg/kg/dose	Day 1 ONLY	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN/Cr/AST /ALT/T bili d. Serum IgG e. CrCl or GFR f. CSF cell count, diff, cytospin g. Local BM eval h. PB for Lestaurtinib PK/PIA (see Section 13.1 for details) i. *OPTIONAL BM for flow MRD, molec. MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m^2/dose BID	Days 1-5	Total daily dose: 6 mg/m^2/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) Dose < 1 MTX: 7.5mg HC: 7.5 mg ARAC: 15 mg ≥ 1 MTX: 8 mg HC: 8 mg ARAC: 16 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (IV MTX)	IV push	20 mg/m^2/dose	Days 8, 15, 22		
Mercaptopurine (MP)	PO/NG	75 mg/m^2/dose See Appendix VI for dosing.	Days 8-28	Should be given on an empty stomach	
Lestaurtinib (LEST)	PO/NG	IR: 5 mg/kg/day divided BID HR: 4.25 mg/kg/day divided BID	Days 2-6	Should be given with food	

Circle Cycle #: 1 3 5 Ht____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	VCR ____mg	DEX __mg __mg	ITT __mg (MTX) __mg (HC) __mg (ARAC)	IV MTX ____mg	MP ____mg	LEST __mg __mg	Studies
				Enter calculated dose above and actual dose administered below						
		20/33[α]/46[α]	1	____mg	__mg __mg	__mg (MTX) __mg (HC) __mg (ARAC)				a*, b, d, f (c, e, g, i)*
			2-5		__mg __mg				__mg __mg	
			6						__mg __mg	
			7							
		(21/34/47)[β]	8				____mg	____mg		b
			9-14							
		(22/35/48)[β]	15				____mg			b
			16-21							
		(23/36/49)[β]	22				____mg			b
			23-28							
			29	**Start next course (Continuation II, Section 4.7.5) the day after Week 49/Day 28 or when blood count parameters are met (whichever occurs later).**						

Comments may be documented on a separate page.

[α] Begin regardless of counts once off G-CSF for at least 48 hrs

[β] For IV MTX/MP: skip week if ANC < 500/μL or plts < 50,000/μL

* Week 20 (Cycle #1) ONLY

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

4.7.4.1 Continuation I (ARM C: IR/HR patients classified as MLL-R)

Modified Continuation I + Lestaurtinib is for IR/HR patients (30 weeks/210 days). Continuation I occurs in five cycles. Cycle #2 lasts 9 weeks, includes the therapy described below and is repeated during Cycle #4. [*Cycle #1 lasts 4 weeks, includes the therapy described previously and is repeated during Cycles #3 and #5*]

Patient name or initials

DOB

*Begin Continuation I when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 30 weeks (Weeks 20-49) and this Therapy Delivery Map is on **three (3)** pages. Cycles 2 and 4 are described below.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg/dose	Day 1 ONLY	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/ BUN/Cr/AST/ ALT/T bili d. Serum IgG e. CrCl or GFR f. CSF cell count, diff, cytospin g. Local BM eval h. PB for Lestaurtinib PK/PIA (see Section 13.1 for details) i. *OPTIONAL BM for flow MRD, molec. MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m²/dose BID	Days 1-5	Total daily dose: 6 mg/m²/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg; HC: 7.5 mg; ARAC: 15 mg ≥ 1: MTX: 8 mg; HC: 8 mg; ARAC: 16 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (IV MTX)	IV push	20 mg/m²/dose	Days 8 & 15		
Mercaptopurine (MP)	PO/NG	75 mg/m²/dose. See Appendix VI.	Days 8-21	Should be given on an empty stomach	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m²/dose	Days 22-26	See page 3 for criteria to receive ETOP/CPM	
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m²/dose	Days 22-26		
Mesna	IV over 30 min followed by CI	150 mg/m²/dose with CPM followed by 150 mg/m²/dose over 4 hrs daily (2 total doses/day)	Days 22-26	See Section 4.7.4 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Days 27 & 45	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	3000 mg/m²/dose q12 hrs x 4 doses total; begin min 48 hrs after G-CSF	Days 43 & 44	See page 3 for criteria to receive HD ARAC; see Section 6.4 regarding administration of eye drops	
Pegaspargase (PEG-ASP)	IM	2500 International units/m²/dose	Day 44	3 hrs after final HD ARAC	
Lestaurtinib (LEST)	PO/NG	IR: 5 mg/kg/day divided BID HR: 4.25 mg/kg/day divided BID	Days 2-6, 27-41 & 45-56	Should be given with food	

Circle Cycle #: 2 4 **Ht____cm** **Wt____kg** **BSA____m²**

Date Due	Date Given	Week	Day	VCR ____mg	DEX ___mg ___mg	ITT ____mg (MTX) ____mg (HC) ____mg (ARAC)	IV MTX ____mg	MP ____mg	LEST ____mg ____mg	Studies
				Enter calculated dose above and actual dose administered below						
		(24/37)α	1	____mg	___mg ___mg	____mg (MTX) ____mg (HC) ____mg (ARAC)				b, d, f
			2		___mg ___mg				___mg ___mg	
			3		___mg ___mg				___mg ___mg	
			4		___mg ___mg				___mg ___mg	
			5		___mg ___mg				___mg ___mg	
			6						___mg ___mg	
			7							
		(25/38)β	8				___mg	___mg		b
			9							
			10							
			11							
			12							
			13							
			14							
		(26/39)β	15				___mg			b
			16							
			17							
			18							
			19							
			20							
			21							c, d

Comments may be documented on a separate page.

α Begin regardless of counts 4 weeks after start of Week 20/33

β For IV MTX/MP: skip week if ANC < 500/µL or platelets < 50,000/µL

4.7.4.1 Continuation I (ARM C: IR/HR patients classified as MLL-R)

Modified Continuation I + Lestaurtinib is for IR/HR patients (30 weeks/210 days). Continuation I occurs in five cycles. Cycle #2 lasts 9 weeks, includes the therapy described below and is repeated during Cycle #4. [*Cycle #1 lasts 4 weeks, includes the therapy described previously and is repeated during Cycles #3 and #5*]

Patient name or initials

DOB

*Begin Continuation I when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course lasts 30 weeks (Weeks 20-49) and this Therapy Delivery Map is on **three (3)** pages. Cycles 2 and 4 are described below.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	0.05 mg/kg/dose	Day 1 ONLY	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN, Cr/AST/ALT/T bili d. Serum IgG e. CrCl or GFR f. CSF cell count, diff, cytospin g. Local BM eval h. PB for Lestaurtinib PK/PIA (see Section 13.1 for details) i. *OPTIONAL BM for flow MRD, molec. MRD & resistance mechanisms.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m²/dose BID	Days 1-5	Total daily dose: 6 mg/m²/day, divided BID	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (years) / Dose < 1: MTX: 7.5mg, HC: 7.5 mg, ARAC: 15 mg ≥ 1: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (IV MTX)	IV push	20 mg/m²/dose	Days 8 & 15		
Mercaptopurine (MP)	PO/NG	75 mg/m²/dose See Appendix VI for dosing.	Days 8-21	Should be given on an empty stomach	
Etoposide (ETOP)	IV over 2 hrs	100 mg/m²/dose	Days 22-26	See below for criteria to receive ETOP/CPM	
Cyclophosphamide (CPM)	IV over 30 min	300 mg/m²/dose	Days 22-26		
Mesna	IV over 30 min followed by CI	150 mg/m²/dose with CPM followed by 150 mg/m²/dose over 4 hrs daily (2 total doses/day)	Days 22-26	See Section 4.7.4 for infusion details	
Filgrastim (G-CSF)	SubQ/IV	5 mcg/kg/dose	Daily beg. Days 27 & 45	Continue until ANC > 1500/µL x 2 days post nadir; stop at least 48 hrs prior to next chemo cycle	
High Dose Cytarabine (HD ARAC)	IV over 3 hrs	3000 mg/m²/dose q12 hrs x 4 doses total; begin min 48 hrs after G-CSF	Days 43 & 44	See below for criteria to receive HD ARAC; see Section 6.4 regarding administration of eye drops	
Pegaspargase (PEG-ASP)	IM	2500 International units/m²/dose	Day 44	3 hrs after final HD ARAC	
Lestaurtinib (LEST)	PO/NG	IR: 5 mg/kg/day divided BID HR: 4.25 mg/kg/day divided BID	Days 2-6, 27-41, 45-56	Should be given with food	

Circle Cycle #: 2 4 **Ht____cm** **Wt_____kg** **BSA_____m²**

Date Due	Date Given	Week	Day	ETOP ___mg	CPM ___mg	MESNA ___mg ___mg	G-CSF ___mcg	HD ARAC ___mg ___mg	PEG-ASP ___IU	LEST ___mg ___mg	Studies
				Enter calculated dose above and actual dose administered below							
		(27/40)α	22	___mg	___mg	___mg ___mg					b
			23	___mg	___mg	___mg ___mg					
			24	___mg	___mg	___mg ___mg					
			25	___mg	___mg	___mg ___mg					
			26	___mg	___mg	___mg ___mg					
			27				___mcg			___mg ___mg	
			28				↓			___mg ___mg	
		28/41	29-35							___mg ___mg	b
		29/42	36-39							___mg ___mg	b
			40-41							___mg ___mg	h
			42								
		(30/43)β	43					__mg __mg			b, d
			44					__mg __mg	___IU		
			45				___mcg			___mg ___mg	
			46-49				↓			___mg ___mg	
		31/44	50-56							___mg ___mg	b
		32/45	57-63								b

Indicate last G-CSF if past Day 63 _____

Comments may be documented on a separate page.

α Begin when ANC > 750/µL & plts > 75,000/µL

β Begin when off G-CSF for at least 48 hrs and ANC > 750/µL & plts > 75,000/µL

4.7.5 Continuation II: Weeks 50-104 (Arm C)

Arm C Continuation II Update as of Amendment #5:
Lestaurtinib will no longer be administered with Continuation II therapy as of Amendment #5. All newly enrolled patients and patients that have not yet reached Continuation II will cease lestaurtinib treatment following Continuation I. Patients currently receiving Continuation II as of Amendment #5 will cease Lestaurtinib as of the activation of the amendment.

To begin Continuation II, patients must have ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hours.

Each cycle of Continuation II lasts 12 weeks and should be repeated until 2 calendar years from diagnosis.

Week 50

VinCRIStine: 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5
IT Methotrexate: < 1 year: 7.5 mg Day 1 ONLY
1 year - < 2 years: 8 mg Day 1 ONLY
≥ 2 years: 10 mg Day 1 ONLY
See Section 5.7 regarding IT dose reduction for patients requiring Ommaya reservoir administration

Weeks 51-53

Methotrexate: 20 mg/m^2/dose PO/NG weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week). Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Week 54

VinCRIStine: 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5

Continue repeating 12 week cycles until 2 years from diagnosis (see below for remaining cycle information).

Weeks 55-57 **Methotrexate:** 20 mg/m^2/dose PO/NG weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week)
Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Week 58 **VinCRIStine:** 0.05 mg/kg/dose IV push over 1 minute or infusion via minibag as per institutional policy Day 1 ONLY
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."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.
Dexamethasone: 6 mg/m^2/day PO/NG/IV divided BID Days 1-5

Weeks 59-61 **Methotrexate:** 20 mg/m^2/dose PO/NG weekly (Day 1 of each week)
Mercaptopurine: 75 mg/m^2/dose PO/NG daily (Days 1-7 of each week).
Administer in the **evening** on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Food or milk delays absorption and decreases the peak concentration. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph). See Appendix VI for dosing guidelines.

Continue repeating 12 week cycles until 2 years from diagnosis (see above for weeks 50-54).

The therapy delivery map (TDM) for Continuation II is on the next page.

4.7.5.1 Continuation II (ARM C: IR/HR patients classified as MLL-R)

Modified Continuation II is for IR/HR patients. (12 week cycles repeated until 2 years from diagnosis). Each cycle is 12 weeks in length and includes the therapy described below.

_____
Patient name or initials

_____
DOB

*Begin Continuation II when ANC > 750/µL and platelets > 75,000/µL and have been off G-CSF for at least 48 hrs. This Course is composed of 12-week cycles that are repeated until 2 calendar years from diagnosis; this Therapy Delivery Map describes one cycle and is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	0.05 mg/kg/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA b. CBC (diff/plt) c. Electrolytes/BUN/Cr/AST/ALT/ T bili d. Serum IgG e. CSF cell count, diff, cytospin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO/NG/IV	3 mg/m²/dose BID	Days 1-5, 29-33 & 57-61	Total daily dose: 6 mg/m²/day, divided BID	
Intrathecal Methotrexate (IT MTX)	IT	Age (years) Dose < 1 7.5 mg 1 - < 2 8 mg ≥ 2 10 mg	Day 1 ONLY	**Note age-based dosing** See Section 5.7 regarding IT dose reduction for pts requiring Ommaya reservoir administration	
Methotrexate (MTX)	PO/NG	20 mg/m²/dose	Days 8, 15, 22, 36, 43, 50, 64, 71 & 78	Hold with IT MTX	
Mercaptopurine (MP)	PO/NG	75 mg/m²/dose See Appendix VI for dosing.	Days 8-28, 36-56 & 64-84	Should be given on an empty stomach	

Cycle # _____ Ht ____cm Wt ____kg BSA ____m²

Date Due	Date Given	Week	Day	VCR ___mg	DEX ___mg ___mg	IT MTX ___mg	PO MTX ___mg	MP ___mg	Studies
				Enter calculated dose above and actual dose administered below					
		50	1	___mg	___mg ___mg	___mg			(a, c, d, e)*, b
			2		___mg ___mg				
			3		___mg ___mg				
			4		___mg ___mg				
			5		___mg ___mg				
			6						
			7						
		51	8				___mg	___mg	
			9-14						
		52	15				___mg		
			16-21						
		53	22				___mg		
			23-28						
		54	29	___mg	___mg ___mg				b
			30-33		___mg ___mg				
			34						
			35						
		55	36				___mg	___mg	
			37-42						
		56	43				___mg		
			44-49						
		57	50				___mg		
			51-56						
		58	57	___mg	___mg ___mg				b
			58-61		___mg ___mg				
			62						
			63						
		59	64				___mg	___mg	
			65-70						
		60	71				___mg		
			72-77						
		61	78				___mg		
			79-84						
			End of Therapy						

Comments may be documented on a separate page. * Start of each 12-week cycle

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND APPENDIX I FOR SUPPORTIVE CARE

5.0 DOSE MODIFICATIONS FOR TOXICITIES

Notify a Study Co-Chair at the time of removing a patient from protocol therapy for toxicity. The drugs are listed in alphabetical order.

5.1 Asparaginase [*E. coli,* Pegaspargase (PEG-Asparaginase) or Erwinia]

Allergy

Because of toxicity concerns with the use of pegaspargase during Induction, patients developing allergic reactions to *E. coli* asparaginase during Induction will receive *Erwinia* asparaginase for each remaining dose of *E. coli* asparaginase. Also, in cases where *E. coli* asparaginase is not available, *Erwinia* asparaginase should be substituted. If *Erwinia* asparaginase is not available, then the remaining doses of *E. coli* asparaginase during Induction should be omitted. If the patient develops a severe allergic reaction to *Erwinia* during Induction, then the remaining doses during Induction should be omitted. Upon completion of Induction, patients should resume therapy with pegaspargase. If allergy subsequently develops to pegaspargase, patients should then receive *Erwinia* asparaginase for any remaining pegaspargase doses. If the patient previously experienced severe allergic reaction to *Erwinia* during Induction, the decision to administer any asparaginase product in the post-Induction period should be carefully weighed by the treating physician.

Local Allergic Reactions (inflammation at injection site, swelling):
Continue administration in the presence of Grade 1 allergy as defined by CTCAE v4.0 (transient flushing or rash; drug fever < 38ºC).

Systemic Allergic Reactions: Discontinuation may be considered for severe Grade 2 or higher allergic reactions as defined by CTCAE v4.0.

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

Anaphylaxis: Discontinue pegaspargase or *E. coli* asparaginase 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.

*Erwinia aspa*raginase has a shorter half *life and* is associated with a shorter duration of asparagine depletion than native *E. coli* asparaginase, with "head-to-head" comparisons of Erwinia and *E. coli* asparaginase, using the same dose and schedule for both preparations, demonstrating a superior outcome, favoring *E. coli* asparaginase.[44,45] Pegaspargase has a longer half-life and is associated with more prolonged asparagine depletion than native *E. coli* asparaginase, but the largest randomized trial comparing weekly native to bi-weekly pegaspargase wasn't powered to detect a difference in outcome.[46] Current COG trials have adopted pegaspargase as the preparation of choice, based on the results of CCG 1962.[47] COG AALL07P2 showed that Erwinia 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 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.

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

Phase(s) of Treatment[1]	Drug(s)	Replacement Schedule for Erwinia asparaginase
Induction therapy (≥ 6 months at diagnosis)	One or more doses of *E. coli* asp (7,500 IU/m^2)	30,000 IU/m^2/dose IM for each remaining dose of *E. coli* asparaginase
Induction therapy (≥ 7 days - < 6 months of age at diagnosis)	One or more doses of *E. coli* asp (6,675 IU/m^2)	27, 000 IU/m^2/dose IM for each remaining dose of *E. coli* asparaginase
Induction therapy (< 7 days of age at diagnosis)	One or more doses of *E. coli* asp (5,000 IU/m^2)	20,000 IU/m^2/dose IM for each remaining dose of *E. coli* asparaginase
Post-Induction therapy	One or more doses of pegaspargase (2,500 IU/m^2)	25,000 IU/m^2/dose IM M/W/F x 6 doses

[1] Patients developing allergy to *E. coli* asparaginase during Induction should receive *Erwinia* asparaginase for each remaining *E. coli* asparaginase during Induction as indicated in the table. These patients should resume therapy with pegaspargase post-Induction. If subsequent allergy develops to pegaspargase, they should receive *Erwininia* asparaginase as outlined in the table.

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

Hyperbilirubinemia: asparaginase may need to be withheld in patients with an elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity. There are no specific guidelines available.

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 (Grade 3-4): Discontinue asparaginase in the presence of hemorrhagic pancreatitis or severe pancreatitis. In the case of mild pancreatitis, asparaginase should be held until symptoms and signs subside, and amylase levels return to normal and then resumed. Severe pancreatitis is a contraindication to additional asparaginase administration.

Thrombosis: Withhold asparaginase until resolved, and treat with appropriate anti-thrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing LMWH or anti-thrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate.

CNS Events (bleed, thrombosis or infarction): Discontinue asparaginase. Treat as appropriate.

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/1.73 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 ARAC for fever if it is likely to have been caused by the ARAC. 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 the cycle with HD ARAC (Induction 3, Intensification 2) has started do not interrupt for uncomplicated myelosuppression; do hold for ANC < 500/μL and severe infection. Do make up missed doses.

Adequate renal function (as defined as creatinine within normal range) is required for the administration of high dose ARAC. 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

Cardiac Toxicity: Discontinue for clinical or echocardiographic evidence of cardiomyopathy (SF < 27% or EF < 50%) or Grade 3-4 LVSD per CTCAE version 4.0.

Note: use the following term to report decreases in the EF or SF: *Cardiac disorders – other.*

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. During Induction, continue with anthracycline administration. Subsequent doses should be given at full dose.

Hyperbilirubinemia:

Direct bilirubin < 1.2 mg/dL	- Full dose
Direct bilirubin 1.2-3.0 mg/dL	- 50% dosage decrease.
Direct bilirubin 3.1-5.0 mg/dL	- 75% dosage decrease.
Direct bilirubin > 5 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 institutional guidelines. Also see https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG guidelines.

Perineal Irritation:
See Appendix I.

5.5 Etoposide (VP-16)

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.

Hypotension: If hypotension develops during infusion, hold infusion and manage blood pressure. When blood pressure is stable, consider resuming infusion at 25%-50% reduction in rate.

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

5.6 Lestaurtinib

While a patient is receiving scheduled doses of lestaurtinib, either of the following adverse events necessitates cessation of lestaurtinib:

- Any Grade 3 or greater non-hematologic toxicity that is at least possibly attributable to lestaurtinib and is of at least 48 hours duration, with the specific exception of: febrile neutropenia, infection, constitutional symptoms (see Section 4.2), mucositis and diaper area skin ulceration.
- Any life-threatening toxicity regardless of attribution and of any duration

Missed doses will not be made up. Lestaurtinib therapy may not resume until the toxicity has resolved to ≤ Grade 2. If the toxicity that caused the cessation is NOT a DLT (as defined in Section 4.2.3), then lestaurtinib therapy may resume without dose modification with the next scheduled dose. If the toxicity that caused the cessation is a DLT, and is the patient's first DLT, then lestaurtinib therapy may resume with a 25% dose reduction with the next scheduled dose. Patients that experience a second DLT after a dose reduction will be required to discontinue lestaurtinib therapy. Dose modification or withholding of doses other than as described in this section is not permitted.

NOTE: A study co-chair should be notified for all lestaurtinib dose modifications.

5.7 Intrathecal Methotrexate/Triple Intrathecal Therapy

Do not withhold dose given on Day 1 of Induction.

Systemic toxicity: The dosage for IT chemotherapy will not be reduced for systemic toxicity (myelosuppression, mucositis, etc). Instead, leucovorin may be used at a dose of 5mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered. IT MTX does have a systemic effect and is cleared by the kidney. Consider omitting MTX in the face of renal failure or severe dysfunction.

Dose modifications following an episode of acute neurotoxicity:

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.[48-53] It is clear however, that CNS prophylaxis is a mandatory component of curative therapy for children with ALL. Effective prophylaxis generally takes two forms; cranial, or less commonly, craniospinal radiation, with a limited number of doses of IT therapy or prolonged IT therapy with either IT MTX or triple IT therapy (MTX, Ara-C and hydrocortisone). For infants, the latter approach is generally used due to high risk of radiation-induced neurotoxicity.

Guidelines are offered for consideration following an acute event. 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 with appropriate laboratory and radiological evaluation.

Many acute events like seizures or episodes of transient hemiparesis, are temporally related to the administration of intrathecal therapy, commonly 9 to 11 days after the IT administration.[54] For patients who return to their "pre-event" status, without residual deficits on 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 one dose of IT MTX, or triple IT therapy. It is also reasonable to include leucovorin rescue at a dose of 5 mg/m^2 q 12 hrs x 2 doses beginning 48 hours after the LP. In the face of multiple 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.

Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture:
Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based doses** that would be given by LP. NOTE: Obstruction to CSF flow may be a contraindication to intrathecal and/or intraventricular therapy.

Viral, bacterial, or fungal meningitis: Omit until resolved.

5.8 High-Dose Methotrexate (HD MTX) and Leucovorin Rescue

[*Please note that* ***HD MTX*** *refers to* IV *MTX* ***4 or 5g/m^2 given over 24*** **hrs**]
Methotrexate levels at 24 hours following HD MTX range from 30-70 µM. The treating physician should be notified of all MTX levels. Levels at 24 hours which exceed 90 µM should lead the physician to carefully monitor subsequent levels and renal function.

HD MTX Infusion Guidelines
See Appendix V for a flowchart of the HD MTX/LCV guidelines.

When IT therapy and HD MTX 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 HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM, as well as nonsteroidal anti-inflammatory agents, proton pump inhibitors, aspirin-containing drugs and penicillins.

Infants receiving therapeutic doses of amphotericin should have that drug withheld on the day HD MTX is administered and for the following 24 hours due to the risk of delayed MTX excretion, renal dysfunction and resultant toxicity.

See Appendix I for supportive care guidelines aimed at reducing the risk of perineal irritation associated with HD MTX administration.

Recommended Prehydration with D5 ¼ NS with 30 mEq NaHCO3/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 min) may be given to raise the urine pH relatively quickly, a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout HD MTX infusion, and for a minimum of 48 hours after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 µM.

Hour 0: MTX 200 mg/m^2 IV mixed in 40 mL/m^2 D5 ¼ NS with 30 mEq NaHCO3/L and infused over 20 minutes. This is followed, immediately, by MTX 3800 mg/m^2 mixed in 2960 mL/m^2 D5 ¼ NS with 30 mEq NaHCO3/L given by continuous IV infusion over the remainder of 24 hours at 125 mL/m^2/hr. Be certain that the HD MTX 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 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. While waiting for the result and 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 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 HD MTX to a patient with this degree of renal impairment, assuming that prolonged excretion can be managed with glucarpidase.

NOTE: For patients who have markedly delayed MTX clearance secondary to renal dysfunction, strongly consider using glucarpidase (carboxypeptidase G_2, Voraxaze™).[55,56] To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at (855) 786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product

availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com.Patients requiring glucarpidase rescue will remain on study.

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
< 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	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 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.

*Alternative prophylaxis with dapsone, aerosolized pentamidine, or atovaquone (30 mg/kg/day if 1-3 mo. or > 2 years, 45 mg/kg/day if between 3 mo. & 2 years) should be considered.

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

Mucositis: For Grade 3-4 mucositis, withhold IV MTX until resolved. Decrease subsequent IV MTX dose by 20%. If subsequent cycle is not associated with Grade 3-4 mucositis, attempt to increase to full dose MTX for next cycle. Considering culturing lesions for herpes simplex if mucositis persists or recurs.

Myelosuppression: If prolonged neutropenia (ANC < 750/µL for more than 7 days) despite discontinuation of TMP/SMX **or** prolonged thrombocytopenia (platelets < 75,000/µL for > 7 days) then hold IV MTX until recovery and then administer IV MTX at full dose. If prolonged myelosuppression recurs then reduce methotrexate dose by 20%.

5.9 Weekly IV or PO/NG Methotrexate (MTX) and 6-Mercaptopurine (6-MP)

Continuation I (ARM A: Weeks 21-23, 25-27, 32-34, 36-38; ARMS B/C: Weeks 21-23, 25-26, 34-36, 38-39, 47-49)

Check counts weekly prior to IV MTX/MP dosing. If ANC < 500/µL or platelets < 50,000/µL, skip that week's therapy (one IV MTX dose and seven daily doses of 6-MP). Do not make up missed weeks. For first episode of a skipped week of IV MTX/MP, resume IV MTX/MP at 100% dosing. For each subsequent episode of a skipped week of IV MTX/MP, resume IV MTX/MP with a 25% reduction in dose. Consider discontinuing TMP/SMZ and starting alternative PCP prophylaxis as per supportive care guidelines in Appendix I. Perform thiopurine pharmacology testing as described below.

ADDITIONAL NOTES for Continuation I:

1) Do not escalate IV MTX/MP above 100% dosing during Continuation I.
2) ARM A:

- For Weeks 24 & 35 VCR/DEX/ITT: Begin regardless of counts 4 weeks after the start of Week 20/31.
- For Week 31 VCR/DEX/ITT: Begin regardless of counts once off GCSF for 48 hours.

3) ARMS B/C:
   - For Weeks 24 & 37 VCR/DEX/ITT (+/-Lestaurtinib): Begin regardless of counts 4 weeks after the start of Week 20/33.
   - For Weeks 33 & 46 VCR/DEX/ITT: Begin regardless of counts once off GCSF for 48 hours.

Continuation II:
Check counts every 4 weeks. If neutrophil count falls below 500/µL or if platelet count falls below 50,000/µL during Continuation II, only MP and MTX will be held until recovery above these levels. For the first drop in ANC or platelets, resume chemotherapy at 100% after ANC is ≥ 750/µL and platelets are ≥ 75,000/µL. If neutrophil count falls below 500/µL or if platelet count falls below 50,000/µL for a second time, discontinue doses until ANC is ≥ 750/µL and platelets are ≥ 75,000/µL. Restart mercaptopurine and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-4 week intervals provided ANC remains ≥ 750/µL and platelets remain ≥ 75,000/µL. Consider discontinuing TMP/SMZ and starting alternative PCP prophylaxis as per supportive care guidelines in Appendix I. If neutrophil count falls below 500/µL or if platelet count falls below 50,000/µL on ≥ 2 occasions during Continuation, perform thiopurine pharmacology testing as described below. Should therapy be withheld for myelosuppression or elevated transaminase, do not "make up" that week. Resume therapy at the correct point, chronologically.

Dose escalation during Continuation II:
For ANC ≥ 1500/µL on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s) alternately increase doses of MTX or MP by 25%. If both MTX and MP are increased once without a fall in ANC, consider noncompliance as a possibility. Noncompliance can be assessed by obtaining sample for RBC thioguanine nucleotides (TGNs). Consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2-4 hours later. This will document whether or not poor absorption contributes to lack of response and may facilitate discussions about noncompliance.

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 total bilirubin. Monitor SGPT/ALT or SGOT/AST and total 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 6MP, especially if red cell meTIMP is elevated. If liver function improves in the absence of MP, consider resuming MP dose at 50% and escalating every 2 weeks as tolerated. Also consider liver biopsy.

Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in SGPT/ALT or SGOT/AST above 5x ULN.

Thiopurine Pharmacology Testing and Dosage Adjustments:
MP and 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 1 variant (non-functional) TPMT allele (i.e., heterozygotes).[57-60] Patients with low TPMT form higher concentrations of the thioguanine nucleotides (TGNs) 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.[61]

There are now CLIA certified tests for TPMT genotype and phenotype, and for meTIMP and TGN measurements.

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 patients 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 patients, 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. NOTE: *Genotyping can be done despite recent transfusions.*

Suggested Dose adjustments in patients with unacceptable myelosuppression:

- If the patient is *homozygous deficient* for TPMT, the thiopurine dose should be *reduced to* 10-20 mg/m^2/day 3 days per week. If the patient is *heterozygous for TPMT and* has experienced significant myelosuppression, the thiopurine dose should be reduced by 30%-50%. 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 patient is homozygous wild-type (high activity) for TPMT, then discontinue TMP/SMZ and use pentamidine or dapsone. For modifications of the oral MP and MTX, see the beginning of this section (5.9).

At the time of clinic visit the treating physician needs to follow-up with the caregiver to ascertain that the patient has been receiving the oral medication per protocol and this information needs to be documented in the patient record.

5.10 Steroids (Dexamethasone and Prednisone)

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. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and ≥ Grade 3 amylase elevation (> 2.0 x ULN).

Osteonecrosis: Do not modify corticosteroid therapy for osteonecrosis (also referred to as avascular necrosis) prior to Continuation. Consider omitting Continuation steroid for osteonecrosis Grade 1 (clinically asymptomatic, radiographic finding only). Omit Continuation steroid for osteonecrosis Grade 2 or greater, and notify Study Chair. Consider resuming Continuation steroid after 6 months if joint symptoms have resolved and if MRI findings have significant improved or normalized.

Varicella: Steroids should be held during active infection except during Induction. Do not hold during incubation period following exposure.

Inability to use oral doses: For prednisone, substitute IV methylprednisolone at 80% of the oral prednisone dose. Note that if substituting prednisolone for prednisone, the doses are the same; prednisone is converted in the liver to prednisolone. For dexamethasone, substitute the IV preparation mg for mg.

Severe infection: Do not hold or discontinue steroids during Induction 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: Steroid dose may be decreased by 50% for severe psychosis.

5.11 **Vincristine**

**** PLEASE USE "BALIS" SCALE FOR GRADING NEUROPATHY (See 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. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out hereditary neuropathy syndromes.

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. Physical therapy may be beneficial

Jaw pain: Treat with analgesics; do not modify vincristine dose.

Hyperbilirubinemia:[62,63]

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

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

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 (such as grasp, rake or reach) or gross motor skills (such as head control, sit, ambulate) without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (such as grasp, rake or reach) or gross motor skills (such as head control, sit, 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 (such as grasp, rake or reach) or gross motor skills (such as head control, sit, ambulate), without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gross and 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.

5.12 Drug Interactions

Lestaurtinib is metabolized by the cytochrome P450 isoform CYP3A4/5. Potent inhibitors of CYP3A4/5 are likely to inhibit lestaurtinib metabolism and increase systemic exposure. Therefore, concomitant treatment with lestaurtinib and cyclosporine, HIV (human immunodeficiency virus) protease inhibitors, and nefazodone (see Appendices II and III for additional details) and the agents listed in the table below should be avoided. It is also likely that inducers of CYP3A4/5, such as dexamethasone and St. John's Wort will reduce the plasma exposure to lestaurtinib. Concomitant administration of these drugs is also discouraged, except for dexamethasone as prescribed in the treatment regimen (see Appendix II for additional details).

In addition, since concurrent use of enzyme inducing anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazepine) with antileukemic therapy has recently 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.[64] Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsant. Azole antifungals (e.g., fluconazole, itraconazole, voriconazole, posaconazole, and ketoconazole) and the macrolide group of antibiotics (e.g., erythromycin, clarithromycin, and azithromycin) may have potent inhibitory effects on drug-metabolizing enzymes, and the doses of some antileukemic drugs (e.g., vincristine, anthracyclines, etoposide) may need to be reduced in some patients on chronic azole antifungals or antibiotics (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 (Keppra) as alternative
Rifampin	Induction of drug metabolizing enzymes	DO NOT USE
Azole Antifungals (fluconazole, itraconazole*, voriconazole, ketoconazole)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS. May need dose reductions of vincristine*, anthracyclines, etoposide, steroids
Macrolide Antibiotics (erythromycin, clarithromycin, azithromycin, troleandomycin)	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.[65,66]

For more complete list of CYP3A4/5 Inhibitors and Inducers see Appendix II. **Please note: patients assigned to receive lestaurtinib should avoid concomitant treatment with CYP3A4/5 Inhibitors or Inducers (see Sections 4.1.2.2 and 4.1.2.3).**

Possible Drug Interactions with 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.

Possible Drug Interactions with High Dose Methotrexate:
When IT therapy and high dose methotrexate are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV methotrexate infusion (hour -6 to +6, with 0 being the start of the methotrexate bolus).

Hold TMP/SMX on the days of high dose methotrexate infusion and for at least 72 hours after the start of the high dose methotrexate infusion and until the methotrexate level is less than 0.4 μM. In the presence of delayed clearance, continue to hold TMP/SMX until methotrexate level is less than 0.1 μM.

Hold any NSAIDs, penicillins, proton pump inhibitors, or aspirin-containing medications on the day of high dose methotrexate infusion and for at least 72 hours after the start of the high dose methotrexate infusion and until the methotrexate level is less than 0.4 μM. In the presence of delayed clearance continue to hold these medications until methotrexate level is less than 0.1 μM.

6.0 DRUG INFORMATION

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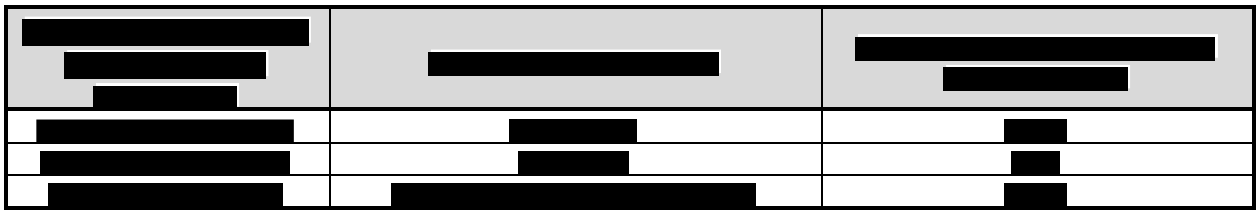

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7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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 per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required and Optional Clinical, Laboratory and Disease Evaluations (X = start of phase)

STUDIES TO BE OBTAINED	Pre-treatment/ Induction	Induction Intensification	Re-Induction	Consolidation	Continuation I	Continuation II	Off Therapy	Relapse, Progression
REQUIRED								
Hx/PE/Ht/Wt/BSA	X	X	X	X	X	Every 12 wks	X	X
CBC/diff/plt	Weekly	Days 1, 8, 15	Days 1, 15	Days 1, 15, 29	Weekly	Every 4 wks	X	X
Electrolytes/BUN/Cr/AST/ALT/T bili	Days 1, 15 & 29	X	X	Days 1, 15	Arm A: Wks 20, 31 Arms B/C: Wks 20, 26, 39	Every 12 wks	X	X
Serum IgG†	Days 1, 15 & 29	Days 1, 15	X	X	See below[1]	Every 12 wks	X	X
Echo or MUGA	X		X				X	
CrCl or GFR (may be estimated using Schwartz method)	X				X		X	
CSF cell count/diff/cytospin	With IT	With IT	With IT	With IT	With IT	With IT	X	X
Local bone marrow evaluation@	X@	X	X		X			X
Bone marrow for AALL08B1 (Columbus)$	X$							X
Blood for lestaurtinib PK/PIA (Hopkins)	X#	X&	X&		X&			
Supportive care measures†	Induction							
OPTIONAL								
Bone marrow for flow MRD, molecular MRD and resistance mechanisms (Hopkins)^	X^	Week 6	Week 10		Week 20			X

@ Pre-treatment local bone marrow evaluation MUST include MLL FISH and standard cytogenetics performed at a COG-certified institutional or commercial laboratory. MLL FISH results must be entered into RDE no later than Day 10. In cases where bone marrow aspirate cannot be performed for medical reasons, or adequate material cannot be obtained, it is permissible to establish the diagnosis using peripheral blood IF there are at least 2500 circulating blasts/µL (i.e., WBC of 10,000 with 25% blasts or WBC of 5000 with 50% blasts).

$ 5 mL in EDTA or heparin. For patients undergoing leukopheresis or manual exchange transfusion, shipment of entire pheresis bag or anticoagulated manually exchanged blood to Columbus is highly encouraged, and may be substituted for bone marrow. IF there are at least 2500 circulating blasts (i.e., WBC of 10,000 with 25% blasts or WBC of 5000 with 50% blasts), peripheral blood (at least 5 mL in EDTA or heparin) may be submitted in addition to bone marrow (highly encouraged) **or** as a substitute for bone marrow (permissible in cases where bone marrow aspirate cannot be performed for medical reasons, or adequate material cannot be obtained).

All patients must have pre-treatment blood sample (3 mL in heparin) sent to Johns Hopkins for baseline measurements.

& 3 mL in heparin. Applies ONLY to MLL-R patients receiving lestaurtinib. See Sections 4.7.1, 4.7.2, 4.7.4 and 13.1 for detailed blood collection schedule.

^ 5 mL in heparin. For patients undergoing leukopheresis or manual exchange transfusion, a portion (at least 5 mL in heparin or other anticoagulant) of the pheresate/exchanged blood may be substituted for bone marrow (in these cases, the pheresis bag/remainder of exchanged blood should be shipped to Columbus). IF there are at least 2,500 circulating blasts/µL (i.e., WBC of 10,000 with 25% blasts or WBC of 5,000 with 50% blasts), peripheral blood (at least 5 mL in heparin) may be submitted in addition to bone marrow (highly encouraged) **or** as a substitute for bone marrow (permissible in cases where bone marrow aspirate cannot be performed for medical reasons, or adequate material cannot be obtained).

† Data regarding serum IgG levels, anti-fungal treatment & hospitalization should be submitted via the eRDES on the Induction Reporting Period CRF (see Appendix I for full details).

[1] Arm A: Weeks 20, 24, 31, 35, 38; Arms B/C: Weeks 20, 24, 26, 30, 33, 37, 39, 43, 46 (see Sections 4.5.4.1, 4.6.4.1, and 4.7.4.1 for details).

See Section 13.0 for specimen handling/shipping instructions.

7.2 Recommended Follow-up

Year One:
-Hx/PE/HT/WT/FOC/CBC diff plt - q month
-MUGA or ECHO/ EKG
-LFT/RFT/UA
-Neuropsychological testing
-Serum IgG q 4 weeks until normal
-Continue TMP/SMZ off therapy for 6 months.
-BM/CSF exams as indicated

Year Two:
-Hx/PE/HT/WT/FOC/CBC diff plt - q 2 months
-MUGA or ECHO/ EKG (if normal, repeat every 2 years for a minimum of 10 years. If abnormal, consider cardiology consultation and more frequent screening)
-LFT/RFT/UA
-Neuropsychological testing
-BM/CSF exams as indicated

Year Three:
-Hx/PE/HT/WT/FOC/CBC diff plt - q 3 months
-LFT/RFT/UA
-Neuropsychological testing
-BM/CSF exams as indicated

Year Four:
-Hx/PE/HT/WT/FOC/CBC diff plt - q 6 months
-LFT/RFT/UA
-Neuropsychological testing
-BM/CSF exams as indicated.

Beginning Year Five
-Hx/PE/HT/WT/FOC/CBC diff plt - q 12 months
-LFT/RFT/UA as indicated
-Neuropsychological testing as indicated

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Failure to achieve remission (defined as M1 marrow; see Section 4.1.1) by end-Induction Intensification (i.e., the beginning of Week 10)
b) Relapse of any site following remission
c) Toxicity or other complications
d) Refusal of further protocol therapy by patient/parent/guardian
e) Completion of planned therapy
f) Physician determines it is in patient's best interest
g) Development of a second malignancy
h) MLL status is indeterminate

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 consent was withdrawn.

8.2 Off Study Criteria

a) Death
b) Lost to follow-up
c) Enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence)
d) Withdrawal of consent for any further data submission
e) Tenth anniversary of study entry

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

Patients will be stratified at the end of Week 5 of Induction, by MLL status and age at diagnosis as defined below:
Standard Risk (SR): MLL-germline (MLL-G)
Intermediate Risk (IR): ≥ 90 days at diagnosis, MLL-rearranged (MLL-R)
High Risk (HR): < 90 days at diagnosis, MLL-R

SR patients will be non-randomly assigned to receive a less intensive chemotherapy regimen without lestaurtinib. A safety/activity phase was conducted separately for the IR and HR patients to identify a safe, tolerable, and biologically active dose of lestaurtinib combined with P9407-based chemotherapy backbone. A tolerable/active dose of lestaurtinib has been identified for IR patients, and the efficacy phase opened to IR patients as of 01/28/11, where they were randomized (1:1) to P9407-based chemotherapy backbone ± lestaurtinib. A tolerable/active dose of lestaurtinib was identified for HR patients, and they proceeded to the randomized efficacy phase on 02/03/12.

9.2 Patient Accrual and Expected Duration of Trial

Original Design: The safety phase will accrue 20 evaluable MLL-R patients (10 IR and 10 HR). The accrual duration for the safety phase is expected to be around 3 months for IR patients (annual accrual rate: 40/year) and 1 year for HR infants (annual accrual rate: 10/year). Thus, it is likely that the IR stratum will proceed to the efficacy phase before the HR stratum. If a tolerable/active dose cannot be identified for the IR stratum, the study will close, since we would be unable to answer the lestaurtinib efficacy question in a reasonable period of time with the small number of patients in the HR stratum. If a tolerable/active dose is identified for the IR stratum but cannot be identified for the HR stratum, the study would remain active until accrual goals are met (n = 162 evaluable MLL-R infants) as described below.

A total of 202 patients will contribute to the efficacy questions for the MLL-R and MLL-G patients. Of these, about 162 are projected to be MLL-R and 40 will be MLL-G (SR). Assuming that both IR and HR strata successfully proceed to the efficacy phase, around 80% of the MLL-R infants (n = 130) will be ≥ 90 days old (IR) and the rest (n = 32) will be < 90 days old at diagnosis (HR).

Hence a total of 222 patients (MLL-G: 40; MLL-R: safety phase – 20, efficacy phase – 162) will be accrued on this study. Accounting for a 10% loss due to early deaths, withdrawal/refusal of protocol therapy, and refusal of the post-Induction randomization, a total of 244 patients will be enrolled during the safety and efficacy phases. Accrual duration for these patients will be around 4.73 to 5 years (adjusting for an initial slow accrual allowing institutions to get IRB approvals for the study), with minimum follow-up of 2 years for all patients. MLL-R patients from 'participating' institutions only will be included in the safety phase. MLL-R patients enrolled from 'nonparticipating' institutions (during the Safety Phase only) will not be eligible to receive Lestaurtinib and will be assigned to the standard chemotherapy arm without Lestaurtinib, after Induction therapy. In addition, while DLT assessments are being made (see Section 9.3.1 for details) for IR/HR patients at the dose level being studied, the study

will continue to accrue patients and during this time MLL-R patients will be assigned to the standard chemotherapy arm without Lestaurtinib, for post Induction therapy. Thus, the total number of patients accrued on this study will likely be greater than the projected 244. However, it is not possible to get a good estimate of the number of additional patients (as described above) that are likely to be enrolled. Hence all statistical analyses to be conducted are based on the initial projection of 222 (244 with a 10% adjustment for losses due to various reasons described above) enrollments on study.

Amended Accrual (Amendment #4):
Tolerable and biologically active doses of lestaurtinib for both the IR and HR arms have been identified. The efficacy phase opened to the IR patients on 01/28/2011 and to the HR patients on 02/03/2012. IR patients are now being randomized (1:1) post-Induction to chemotherapy ± lestaurtinib at 5 mg/kg/day and HR patients at 4.25 mg/kg/day.

A total of 52 MLL-R patients (19 HR; 33 IR) were accrued to the safety phase, since HR and IR patients continued to enroll to the non-lestaurtinib arm during DLT assessments and since patients enrolled at non-Phase 1(+) institutions were not eligible to receive lestaurtinib during the safety phase. The overall target accrual has been increased to account for ineligibles, inevaluables, and the higher than expected number of patients enrolled during the safety phase.

Hence, the modified total accrual for this study is 286 patients (safety phase: 60; efficacy phase: 162 (MLL-R only); MLL-G: 64). Accounting for a 10% loss due to early deaths, withdrawal/refusal of protocol therapy, and refusal of the post-Induction randomization, a total of 315 patients will be enrolled during the safety and efficacy phases.

Patients accrued during the safety phase will not contribute to the efficacy questions. Thus, the increased accrual will not impact the efficacy analyses, and the number of patients required (i.e., 162 eligible/evaluable MLL-R) to answer the efficacy questions will not change.

Amended Accrual (Amendment #5):
The primary objective of AALL0631 has been revised to estimate the 3-year EFS for infants with MLL-R treated with chemotherapy plus the FLT3 inhibitor lestaurtinib (Arm C) at DL2. This will include 10 evaluable patients from the safety phase assigned to DL2, 30 patients randomized to Arm C during the efficacy phase (pre-Amendment #5), and 40 patients non-randomly assigned to lestaurtinib post-Amendment #5. A total of 80 MLL-R patients will be treated on Arm C (chemotherapy + lestaurtinib) to answer the revised primary objective on AALL0631.

Secondary objectives include comparison of the 3-year EFS of infants with MLL-R ALL treated with chemotherapy plus the FLT3 inhibitor lestaurtinib (Arm C) at DL2 to all MLL-R patients treated with chemotherapy alone (Arm B). This will include a total of 55 patients treated on Arm B: 25 from the safety phase and 30 randomized to Arm B during the efficacy phase pre-Amendment #5.

A total of 80 and 55 MLL-R patients will be enrolled on Arm C and Arm B, respectively, to answer the revised primary and secondary objectives on AALL0631. MLL-G patients will continue to enroll on the study at an expected rate of 13 patients per year. Hence, the modified total accrual on this study is 220 patients (safety phase: 60; post-safety phase (MLL-R only): 100; MLL-G: 60). To account for a 10% loss due to ineligibles, early deaths, withdrawals, and refusal of post-Induction therapy, a total of 242 patients will be enrolled on AALL0631 prior to June 2014, anticipated closure date to enrollment due to limited supply of lestaurtinib.

9.3 Statistical Analysis Methods

9.3.1 Safety / Activity Phase

The dose finding (lestaurtinib) part of the study was restricted to the first 2 courses of post-Induction therapy (Induction Intensification and Re-Induction) for the MLL-R patients. The MLL-R patients were stratified according to age at diagnosis (< 90 days old versus ≥ 90 days old). Dose finding was conducted separately for each of the strata. The schema describing the design is detailed in Section 4.2.1 with the toxicities targeted in the safety phase, detailed in Section 4.2.3.

9.3.2 Efficacy Phase

Design Prior to Amendment #5

The primary objective of this study is to compare 3-year EFS of MLL-R infants randomized to a modified P9407 backbone +/- lestaurtinib. All randomized patients will be included in the intent-to-treat efficacy analyses. Event-free survival time will be calculated from the time of randomization, which is just prior to beginning Induction Intensification (see Section 3.1.6). Only if the lestaurtinib arm results in a significant improvement in EFS will it be considered as the superior regimen. Hence 1-sided tests will be used to compare EFS between the 2 arms. The baseline 3-year EFS for these patients on the P9407 backbone is around 50%. Power calculations are based on a 1-sided log rank test (alpha = 0.15) with 5 planned analyses of the data for interim monitoring purposes. The efficacy stopping boundaries are based on the alpha × $(\text{time})^2$ spending function. The study will also be monitored for futility. The lower boundaries are based on repeated testing the alternative hypothesis at the 0.005 level.[67] This monitoring rule can be applied to any interim analysis schedule and maintains the overall significance level of 0.05 approximately. The comparative analyses of regimen outcome will occur at approximately 20%, 40%, 60%, 80%, and 100% of the projected combined EFS event horizon for the overall randomized group.

For the purpose of sample size and power calculations a significant difference is assumed to be an improvement in outcome from 50% EFS at 3 years to 65% EFS. This represents a relative EFS event reduction of approximately 38% for the better regimen (HR = 1.6). An event horizon of 69 EFS events was calculated using the previous EFS outcome assumptions. The cumulative power to detect a difference by the last (fifth) interim analysis is 80.3%. Should a difference of that relative hazard size exist, there is a 22% chance of stopping at the second interim analysis, and 65% chance of stopping at the fourth interim analysis. The monitoring boundaries (for efficacy and futility) are given in the table below.

Looks	# of events	Information	Upper Boundary (Z value)	Lower Boundary (Z value)
1	14	20%	2.5121	-1.6856
2	28	40%	2.0358	-1.3172
3	41	60%	1.7022	-1.0529
4	55	80%	1.4179	-0.8122
5	69	100%	1.1573	1.1573

Revised Design as of Amendment #5

The primary objective of AALL0631 is to estimate the 3-year EFS of those patients treated on Arm C (chemo + lestaurtinib) at DL2 from both the safety and the efficacy phases. A total of 80 patients on Arm C would allow estimation of EFS with a maximum standard error of 5.6%. A one-sided 95% confidence interval for EFS will be constructed. If the 3-year EFS is 50%, the lower limit of the 95% confidence interval will be 40.8%. If the true 3-year EFS is 65%, the lower limit of the confidence interval will be 56.2%.

The secondary objective is to assess the effect of lestaurtinib by comparing patients on Arm C (chemo + lestaurtinib) to those assigned to Arm B (chemo only). Using a one-sided log rank test with 135 patients (55 on Arm B; 80 on Arm C), alpha=15%, and minimum follow-up of 3 years, there is 82% power to detect an improvement in 3-year EFS from 50% to 65% (HR=0.62).

9.3.3 Toxicity Monitoring

The study will be closely monitored for toxicities and adverse events due to the addition of lestaurtinib to the P9407 based chemotherapy backbone. Specific criteria for dose adjustments of lestaurtinib are described in the dose modifications section of the protocol. All toxicities related to lestaurtinib, dose adjustments of lestaurtinib and delays in subsequent therapy due to lestaurtinib will be required to be reported immediately via the RDE. We will also require reporting of the number of prescribed lestaurtinib doses each patient receives during each reporting period. These data will be used to calculate the percentage of patients that are not able to receive at least 75% of the prescribed doses of lestaurtinib during each reporting period. If a specific course is associated with a high percentage of patients unable to receive 75% of the prescribed doses, this may indicate a problem with the tolerability of lestaurtinib in the context of that specific course. The Study Chairs will closely monitor patterns of lestaurtinib toxicity during each reporting period, and amend the study appropriately if toxicity appears to be excessive for one or more of them. Section 4.2.3 describes the DLTs applicable to the safety/activity phase.

Pre-Amendment #5:

Analysis of toxicities associated with lestaurtinib will include all patients who receive at least one dose of drug. Incidence of Grade 3/4 non-hematologic toxicities (infection and AST/ALT) will be compared between the two randomized arms (starting from Induction Intensification therapy Week 6), at the time of each interim monitoring analysis for efficacy. Baseline incidence of infections for the standard arm (P9407 chemotherapy backbone) is expected to be around 30% (data from P9407). A total of 162 patients (81 on each arm), would give 80% power to detect a difference in infection rates between the two arms (30% Std vs. 50% Std + lestaurtinib) using a one-sided Z-test of proportion, alpha = 5%. The study will be monitored for excessive infections on the lestaurtinib arm compared to the standard backbone therapy. The timepoints for sequential monitoring will coincide with the times of the reporting to the COG Data and Safety Monitoring Committee. Interim monitoring looks will occur every six months for the first 2 years of accrual to the efficacy phase, followed by yearly looks. The monitoring boundaries for the projected 5 looks using an alpha x $(\text{time})^2$ spending function are given below.

Look	Time point	Monitoring Boundary	*P*-value
1	6 months	2.8782	0.002
2	12 months	2.4702	0.008
3	18 months	2.2009	0.018
4	24 months	1.9818	0.032
5	36 months	1.7902	0.050

The baseline incidence rate of Grade 3/4 AST/ALT on P9407 on Re-Induction or later part of therapy is around 9%. The incidence of AST/ALT will be compared between the standard and standard plus lestaurtinib arms. A total sample size of 162 gives 80% power to detect a difference in AST/ALT rates (9% Std. vs. 24% Std. + lestaurtinib) using a one-sided Z-test of proportions, with an alpha of 5%. Sequential monitoring plan will be the same as that detailed above for infections.

Toxic death rates on P9407 on Re-Induction or later part of therapy was around 3%. The toxic death rate will be compared between the standard and standard plus lestaurtinib arms. A total sample size of 162 gives 80% power to detect a difference in toxic death rates (3% Std. vs. 14% Std. + lestaurtinib) using a one-sided Z-test of proportions, with an alpha of 5%. Sequential monitoring plan will be the same as that detailed above for infections.

Amendment #5:
Grade 3/4 non-hematologic toxicities (infection and AST/ALT) will continue to be monitored closely and reported (by stratum) biannually to the COG Data and Safety Monitoring Committee during the time of the study reports.

9.3.4 Toxic Death Monitoring
Toxic deaths on the amended Induction therapy will be closely monitored. Deaths will be counted afresh after the modified Induction therapy goes into effect. At the time of this amendment, a total of 26 patients have enrolled onstudy (Less than 30 days old at diagnosis: 2; Greater than or equal to 30 days old at diagnosis: 24). Of the remaining planned accrual of 218 patients, it is projected (based on the age distribution in P9407 Cohort 3) that 6 patients will be less than 30 days old and 212 will be ≥ 30 days old at diagnosis.

Less than 30 days old at diagnosis:
Approximately 6 patients in this age group will be enrolled on the modified induction regimen. On 9407 Cohort 3, there was one death among 5 patients in this age group. Due to the small sample size, it is not possible to have formal statistical rules for monitoring deaths. If 2 deaths occur (on the modified Induction therapy), the study accrual to patients < 30 days old at diagnosis will be temporarily suspended; the data will be closely reviewed before a decision is made on whether to permanently close accrual to this age group.

Greater than or equal to 30 days old at diagnosis:
The 212 patients expected to be enrolled in this age group on the modified Induction therapy, will be included in the continuous monitoring plan detailed below. The study will be temporarily closed for detailed review if:

# cumulative toxic deaths	# of Patients on Study
≥ 4	1-50
≥ 8	51-100

The modified Induction regimen will be deemed too toxic if there are 15 or more toxic deaths at any time among the 212 patients. The probability of declaring the Induction regimen too toxic is 97%, 83%, 50%, 16%, and 1.2% when the true toxic death rate is 10%, 8%, 6%, 4%, and 2%, respectively.

9.3.5 Supportive Care for Fungal Infections
Data will be collected (in eRDE on the reporting period CRF) during Induction on the prophylactic treatment given for prevention of fungal infections. Details will also be collected on empiric treatment given for patients with possible fungal infections. These will be summarized using descriptive statistics. Proportion of infants who received prophylactic treatment, empiric treatment and IVIG will be determined. Mean serum IgG levels (Days 1 and 15 of Induction) will be calculated. Mean number of days hospitalized during Induction until count recovery will also be computed.

9.3.6 Outcome for Standard Risk Patients

The outcome for SR patients (MLL-G) will be described. A sample of 60 patients will allow estimation of 3-year EFS with a maximum standard error of 6.5%. The outcome for these patients will be informally compared with that of MLL-G patients on P9407.

9.3.7 Correlative Biology Studies

The correlative biology studies listed in the secondary objectives are described in Sections 14.1 – 14.5. Analyses to be performed are detailed in each of these sections. As detailed in Section 14.4, MRD will be measured in patients at Weeks 6, 10 and 20 of chemotherapy and at the time of relapse. These are optional studies and, hence, it is difficult to estimate how many patients will have MRD measured at each of these timepoints. Hence, correlation between MRD and outcome will be described in this population. Cox regression will be utilized to correlate MRD values with 3 year EFS as defined in Section 9.3.2.

9.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	16	25	41
Not Hispanic or Latino	87	114	201
Ethnic Category: Total of all subjects	103	139	242
Racial Category			
American Indian or Alaskan Native	2	4	6
Asian	4	9	13
Black or African American	4	11	15
Native Hawaiian or other Pacific Islander	0	0	0
White	93	115	208
Racial Category: Total of all subjects	103	139	242

This distribution was derived from P9407.

10.0 EVALUATION CRITERIA

10.1 **Common Terminology Criteria for Adverse Events (CTCAE)**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning April 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and a copy can be downloaded from the CTEP web site (http://ctep.cancer.gov).

10.2 **Response Criteria**

See definitions in Section 4.1.1.

11.0 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. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

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 via AdEERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

11.3 Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria (CTCAE)* ***[use version 4, beginning 04/01/11]***. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE.*

Step 3: *Determine the attribution of adverse event in relation to the protocol therapy.* Attribution categories are: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.*

For investigational agents that are not commercially available and are being studied under a company's IND or an investigator held IND, expected AEs are usually based on the Investigator's Brochure.

Guidance on expectedness of the agent is provided in the Drug Information Section of this protocol.

Step 5: *Review Tables A and/or B in this section to determine if:*

- *there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or*
- *there are any protocol-specific exceptions to the reporting requirements.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent, a commercial agent, or a combination of investigational and commercial agents.*

Note: If the patient received at least one dose of investigational agent, follow the guidelines in Table A. If no investigational agent was administered, follow the guidelines in Table B.

11.4 Reporting methods

- The reporting methods described below are specific for clinical trials evaluating agents for which the IND is held by COG, an investigator, or a pharmaceutical company. It is important to note that these procedures differ slightly from those used for reporting AEs for clinical trials for which CTEP holds the IND.

- Use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov.

  An AdEERS report must be submitted by the following method:

  - Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm

- Fax or email supporting documentation **for AEs related to investigational agents** to the Children's Oncology Group (fax # 626-303-1768; email: COGAdEERS@childrensoncologygroup.org; Attention: COG AdEERS Coordinator).

- **DO NOT send the supporting documentation for AEs related to commercial agents to the NCI.** Fax this material to COG (fax # 626-303-1768; attention: COG AdEERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**

- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.5 When to report an event in an expedited manner

- Some adverse events require notification **within 24 hours** (refer to Table A) via e-mail to the COG AdEERS Coordinator.
- Submit the report **within 5 calendar days** of learning of the event.

11.6 Other recipients of adverse event reports

COG will forward reports and supporting documentation to the Study Chair, to the drug company (for industry sponsored trials) and to the FDA (when COG holds the IND).

Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

11.7 Reporting of Adverse Events for investigational agents

Reporting requirements are provided in Table A. The investigational agent used in this study is Lestaurtinib (CEP-701; IND#76431); COG is the IND holder.

Table A

Phase 2 and 3 Trials and COG Group-wide Pilot Studies utilizing an Agent under a CTEP IND or a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4[3] & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unex-pected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unex-pected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days	5 Calendar Days	Not Required	**24-Hour**; 5 Calendar Days	5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:**

AdEERS 24-hour notification (via AdEERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in Non-CTEP IND studies) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 5 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization (see exceptions below
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

[3] Please see exceptions below under section entitled "Additional Instructions or Exceptions."

March 2005

Note: All deaths on study require timely reporting to COG via RDE regardless of causality. Attribution to treatment or other cause must be provided.

- **Expedited AE reporting timelines defined:**
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via e-mail to COG AE Coordinator within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete AdEERS report on the AE must be submitted within 5 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

- Protocol specific reporting of AEs, in addition to the AdEERS requirements, are to be entered in the COG remote data entry system.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND:

- **Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via AdEERS per the timelines outlined in the table above.**

- **Grades 1-4 myelosuppression do not require expedited reporting.**

11.8 Reporting of Adverse Events for commercial agents – AdEERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study.
Commercial reporting requirements are provided in Table B.

COG requires the AdEERS report to be submitted **within 5 calendar days** of learning of the event.

Table B

Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

AdEERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via AdEERS.

11.9 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for AdEERS reporting.

The NCI defines both routine and expedited AE reporting. Use CTCAE version 4.0 beginning 04/01/11. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include:

- Grades 3 and higher non-hematologic adverse events;
- Grades 3 and higher hematologic adverse events that result in a delay in therapy greater than one (1) week;
- All adverse events that meet the requirements for filing an AdEERS report as per Section 11.

12.0 RECORDS AND REPORTING

12.1 Categories of Research Records

Computerized Information Electronically Submitted: all computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet posted on the COG web site, which includes a submission schedule.

12.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

13.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

13.1 **Blood for Lestaurtinib PK/PIA** (*required*)

IMPORTANT NOTE: Submission of a pre-treatment blood sample is required for all patients as part of the baseline evaluations. All additional samples are required ONLY for MLL-R patients receiving lestaurtinib.

Collection Schedule (Part 1)

Treatment Block	Induction*	Induction Intensification			Re-Induction				Continuation I (Cycle 2 only)	Total Vol. of Blood (mL)
Preferred Day	1	20 (baseline)	24	27	5 (baseline)	9	12	19	40	27
Acceptable Days	Prior to Day 1	18, 19	23, 25	26, 28	3, 4	7, 8	11, 13	18, 20	39, 41	

* Pre-treatment sample is required for ALL patients

Collection Schedule (Part 2)

Treatment Block	Induction*	Induction Intensification		Re-Induction	Continuation I (Cycle 2 only)	Total Vol. of Blood (mL)
Preferred Day	1	20 (baseline)	27	19	40	15
Acceptable Days	Prior to Day 1	18, 19	26, 28	18, 20	39, 41	

* Pre-treatment sample is required for ALL patients

At each time point, 3 mL of blood must be drawn into green-top (heparin) Vacutainer(s). Each blood collection tube must be labeled as "Block ____, Day: ____ PK/PIA sample" with patient initials, COG registration number, sample date and collection time recorded to the nearest minute using a 24-hour clock. A completed AALL0631 Specimen Transmittal Form must accompany the sample(s) when shipped. Any missing samples, and samples not drawn, must be noted on the Specimen Transmittal Form. Samples should be maintained at room temperature (no refrigeration or icing of samples is necessary) and shipped via overnight courier service to:

Dr. Patrick Brown
Johns Hopkins Oncology
Cancer Research Building I, Room 276
1650 Orleans Street
Baltimore, MD 21231
Laboratory phone: 410-955-8688
Pager no: 410-434-0732
E-mail: pbrown2@jhmi.edu

Samples can be shipped 7 days a week. Saturday deliveries are permissible. If a Saturday delivery is required, please notify Dr. Brown of the planned shipment via pager (410-434-0732) PRIOR to the time of shipment and clearly mark the package "For Saturday Delivery".

If parent/guardian consents, the discarded cell pellet will be used for correlative biology studies as detailed in Section 14.0.

13.2 **Bone Marrow for AALL08B1** (*required*)

For a patient to be eligible for this study, they must have been enrolled on either AALL08B1, and bone marrow (or a suitable substitute, as described below) must be submitted to the COG ALL Reference

Laboratory in Columbus prior to initiation of treatment and at the time of relapse or disease progression. Please refer to the classification study protocol for comprehensive sample requirements and instructions.

13.3 Bone Marrow for Flow MRD, Molecular MRD and Resistance Mechanisms (*optional*)

Bone marrow aspiration must be performed on all patients prior to initiation of treatment, and at other times as noted in Section 7.1 for local evaluation. If parent/guardian consents, bone marrow should also be submitted for MRD and resistance mechanism studies. At least 5 mL of marrow should be transferred to green-top (heparin) Vacutainer(s). All of the studies will be performed on the same bone marrow sample.

IF there are at least 2500 circulating blasts/µL (i.e., WBC of 10,000 with 25% blasts or WBC of 5000 with 50% blasts), **peripheral blood** (at least 5 mL in green top (heparin) Vacutainer(s)) may be submitted as a substitute for the pre-treatment or relapse/progression bone marrow samples (permissible in cases where bone marrow aspirate cannot be performed for medical reasons, or adequate material cannot be obtained).

For patients undergoing **leukopheresis**, the submission of a portion (at least 5 mL) of the anticoagulated pheresate is acceptable and may be substituted for the pre-treatment or relapse/progression bone marrow samples. In these cases, the pheresis bag should be submitted to Columbus for AALL08B1 (see Section 13.2).

For patients undergoing **manual exchange transfusion**, a portion (at least 5 mL) of the manually exchanged anticoagulated blood is acceptable and may be submitted for any of the pre-treatment or relapse/progression bone marrow samples. The remainder of the exchanged blood volume should be submitted to Columbus for AALL08B1 (see Section 13.2).

Each specimen must be labeled with time point in therapy, patient initials, COG registration number, and sample date and collection time recorded to the nearest minute using a 24-hour clock. A completed AALL0631 Specimen Transmittal Form must accompany the sample(s) when shipped. Samples should be maintained at room temperature (no refrigeration or icing of sample is necessary) and shipped via overnight courier service to:

Dr. Patrick Brown
Johns Hopkins Oncology
Cancer Research Building I, Room 276
1650 Orleans Street
Baltimore, MD 21231
Laboratory phone: 410-955-8688
Pager no: 410-434-0732
E-mail: pbrown2@jhmi.edu

Samples can be shipped 7 days a week. Saturday deliveries are permissible. If a Saturday delivery is required, please notify Dr. Brown of the planned shipment via pager (410-434-0732) PRIOR to the time of shipment and clearly mark the package "For Saturday Delivery".

14.0 DESCRIPTION OF CORRELATIVE LABORATORY ASSAYS

14.1 Lestaurtinib Pharmacokinetic (PK)/Plasma Inhibitory Activity (PIA) Assay

Plasma will be separated by centrifugation from 3 mL blood samples collected during lestaurtinib administration and cryopreserved. Aliquots of 4 x 106 TF1/ITD cells (human AML cell line transfected with FLT3/ITD construct) will then be incubated for 1 hour with 0.5 mL of plasma from each timepoint.

The cells will then be washed, lysed and analyzed for FLT3 phosphorylation by FLT3 immunoprecipitation and sequential immunoblotting with 4G10 anti-phosphotyrosine antibody and anti-FLT3 antibody. Densitometric analysis will be used to calculate the PIA (the percent inhibition of FLT3 phosphorylation of each timepoint relative to the pre-treatment sample). These results will be used to determine whether a given dose of lestaurtinib is biologically active. Another 0.1 mL of plasma from the same timepoints will be used to measure the levels of plasma AGP and albumin using standardized radial immunodiffusion kits from Kent Laboratories (will give quantitative levels in mg/dL plasma). We will plot PIA vs. PK level for each data point. If a consistent relationship is seen, future studies could use PK as a simpler surrogate for biologic activity. Measurement of albumin and AGP levels, in conjunction with review of clinical data from the trial, will allow other variables to be incorporated, so that an attempt can be made to develop a predictive model of PIA using these readily available inputs in future studies. If these efforts fail to establish a reliable model of PIA, then future trials would need to continue using the measurement of PIA as described here as the best means of assessing FLT3 inhibition.

14.2 Correlating Clinical Responses with PIA and In Vitro Lestaurtinib Sensitivity

The PIA (expressed as percent inhibition of FLT3 phosphorylation relative to the pretreatment sample) at trough timepoints will be determined for each patient as described in Section 14.1. For each patient, if a majority of available trough plasma samples demonstrate a PIA of ≥ 90%, then, for the purpose of our analysis, "adequate" PIA will have been achieved.

For each patient, an "expected response" will be determined based on presence or absence of the criteria for lestaurtinib sensitivity and adequate PIA (see table). The clinical responses to be considered will be (1) remission status at end of Induction and end of Induction Intensification, (2) presence or absence of MRD at end of Induction and end of Induction Intensification, and (3) 3-year EFS.

In vitro sensitivity	Adequate PIA	Expected response?
+	+	Y
+	-	N
-	+	N
-	-	N

Table 2

14.3 Determining Mechanisms of Resistance to Lestaurtinib

We have already discussed obtaining bone marrow from patients at study entry and using the MTT cytotoxicity assay to define each patient's pre-treatment *in vitro* lestaurtinib sensitivity (Section 14.2). Mononuclear cells will also be isolated from bone marrow samples obtained at other timepoints during therapy, at the time of progressive disease in patients who do not respond, and at the time of relapse in patients who initially respond. We will perform MTT cytotoxicity assays and define these post-treatment samples as "sensitive" or "resistant" to lestaurtinib using the same criteria as described in Section 14.2.

We will investigate mechanisms of **primary resistance** to lestaurtinib using samples that were determined in Section 14.2 to be resistant (or sensitive, for comparison) at the time of study entry. One potential mechanism of resistance is (1) *lack of FLT3 protein expression or constitutive activation*. We will isolate total RNA from each sample and perform quantitative PCR (qPCR) analysis of FLT3 expression relative to the housekeeping gene GAPDH. We will also examine FLT3 expression and constitutive (ligand-independent) phosphorylation/activation at the protein level by performing immunoprecipitation (IP) on clarified whole cell lysate (WCL) with anti-FLT3 antibody, followed by acrylamide gel electrophoresis and sequential immunoblotting (IB) with 4G10 anti-phosphotyrosine (anti-pY) antibody (to assess receptor activation) and anti-FLT3 antibody (to ensure equal loading). Another potential mechanism is (2) *primary (i.e., pre-existing) resistance of the activated FLT3 receptor to inhibition by lestaurtinib*. While none of the samples we have tested to date with either of the 2 major

types of FLT3 mutations (ITD and PM) have demonstrated this type of primary resistance, it is possible that we may find novel variants which do. We will extract WCL from cells before and after 1 hour of exposure to lestaurtinib (50 nM, which is sufficient to inhibit FLT3 phosphorylation), then perform anti-FLT3 IP and sequential 4G10 anti-pY and anti-FLT3 IB. If we find a sample where FLT3 phosphorylation is not inhibited under these conditions, we will reverse transcribe total RNA to cDNA, and use a series of 5 PCR primer sets to amplify the coding region of FLT3. We will then directly sequence these PCR products to look for novel mutations that may mediate primary resistance to lestaurtinib. A third possible mechanism is (3) *FLT3-independent activation of downstream signaling pathways*. We have seen persistent activation of MAPK and STAT5 in lestaurtinib-resistant pediatric and adult AML samples with FLT3 activating mutations despite potent inhibition of FLT3 phosphorylation.[14,38] We will extract WCL from cells before and after 1 hour of exposure to lestaurtinib, which will be electrophoresed on acrylamide gel and then immunoblotted sequentially with anti-phospho STAT5, MAPK and AKT followed by anti-total STAT5, MAPK and AKT (loading controls). If persistent activation in 1 or more of these is seen, this could signal the presence of mutations in upstream signaling proteins involved in these pathways. We will reverse transcribe total RNA to cDNA for these samples, and then interrogate them for known mutations of upstream oncogenes (e.g., mutations in RAS, PTEN or JAK2 as a cause of persistent activation of MAPK, AKT or STAT5, respectively, using screening methods appropriate for each particular mutation). Any mutations discovered will be confirmed by sequencing using the original RNA and genomic DNA.

Patients whose leukemia cells develop *in vitro* resistance after demonstrating *in vitro* sensitivity at study entry will be examined for potential mechanisms of **acquired resistance** to lestaurtinib, including: (1) *Loss of expression of activated FLT3*, which we will examine using PCR screens for FLT3/ITD and FLT3/PM mutations, in addition to qPCR and IP/IB assays of FLT3 RNA expression and FLT3 protein expression and activation. An inherently FLT3-resistant subclone that accounted for a small percentage of leukemia cells at study entry emerges as the dominant clone under the selective pressure of FLT3 inhibition (clonal evolution). We may see, for example, that leukemia cells that develop *in vitro* resistance express significantly lower levels of FLT3 RNA by qPCR, and/or activated FLT3 protein by IP/IB, and/or mutant FLT3 RNA vs. wild-type RNA by PCR (including loss of expression of the FLT3 mutation entirely). These types of changes in expression have been seen in published studies of paired diagnostic and relapse FLT3/ITD+ adult AML samples, even without the selective pressure of FLT3 inhibitor therapy.[68] (2) *Development of resistance of the activated FLT3 receptor to inhibition by lestaurtinib,* due to acquisition of a mutation in the kinase domain of FLT3 that decreases the affinity of binding of the FLT3 inhibitor to the ATP-binding pocket of the receptor. Similar mutations were discovered in a majority of patients with CML in blast crisis who initially responded to imatinib, then relapsed.[69] Mutations in the ATP-binding domain FLT3 have also been discovered in cell lines that developed resistance to FLT3 inhibitors under the pressure of exposure to FLT3 inhibitors in culture.[70,71] We will directly sequence the ATP-binding domain of FLT3 in samples that develop *in vitro* resistance to detect the acquisition of a mutation. If a mutation is discovered, we will first confirm that it has indeed been acquired during therapy by sequencing the relevant portion of FLT3 in the same patient's pre-treatment sample. Finally, FLT3 IP/IB before and after treatment of the cells with lestaurtinib will be done to determine whether the acquired mutations result in increased resistance to inhibition of FLT3 phosphorylation, compared to the same studies performed on the patient's leukemia cells obtained at study entry. (3) *Development of FLT3-independent activation of downstream signaling pathways,* due to mutations in upstream signaling proteins. We will use IB of WCL from cells before and after exposure to lestaurtinib to detect whether the development of persistent activation of downstream targets including MAPK, STAT5 and AKT may be responsible for the acquired resistance. Follow-up directed mutational analysis will be performed if such a case is discovered.

It is possible that the leukemia cells from a patient that initially demonstrates a clinical response to the combination of lestaurtinib and chemotherapy, but then progresses or relapses, will retain *in vitro*

sensitivity to lestaurtinib at the time of progression or relapse. By analyzing the results of the pharmacokinetic (PK), FLT3 PIA, and plasma protein binding assays (AGP, albumin) described in Section 14.1, we may be able to gain insight into such cases. If these data show, for example, inadequate PIA and low PK levels, this may suggest non-compliance with the prescribed lestaurtinib therapy, decreased intestinal lestaurtinib absorption, or increased lestaurtinib clearance (due to Induction of hepatic CYP3A4, which is primarily responsible for metabolism of lestaurtinib, for example). If the data show inadequate PIA but relatively high PK levels, then increased plasma binding protein levels may be responsible, a possibility that is assessable via examination of the measured AGP and albumin levels.

14.4 Minimal Residual Disease (MRD) Testing

MRD assessments by multiparameter flow cytometry and by quantitative RT-PCR are included as optional evaluations at Week 6, Week 10, Week 20 (MLL-G/MLL-R), and off therapy.

14.5 Gene Expression Analysis

These studies will utilize samples submitted to the COG ALL Reference Laboratory in Columbus as part of AALL08B1 (see Section 13.2). Gene expression arrays will be using RNA isolated from sterile, viable cryopreserved leukemic cell suspensions prepared from aspirated bone marrow and peripheral blood samples that had been stored at -135ºC. RNA will be amplified with the Affymetrix One Round labeling kit. Data will be analyzed using various statistical and computational methods, in collaboration between the UNM High Performance Computing Center and the COG Statistical Core. Dr. Cheryl Willman at the University of New Mexico has grant funding for these studies (NCI U01CA114762; Strategic Partnerships to Evaluate Cancer Signatures: Leukemia Signatures for Risk Classification and Targeting). The results of gene expression profiling will be correlated with the functional biochemical assays of sensitivity or resistance to lestaurtinib described in Section 14.3 in an attempt to develop gene expression profiles predictive of sensitivity or resistance to this new agent. The results will also be used in an attempt to extend and validate the novel molecular classification scheme we have developed for infant leukemia, as described in Section 2.7.5.

APPENDIX I: SUPPORTIVE CARE GUIDELINES

General

These are provided for institutional consideration. Investigator discretion should be used, and individual considerations made for specific patient situations and institutional practices. Study Chairs must be notified of any Serious Adverse Events, an Investigator's decision to deviate in a major way from protocol directed therapy, or a patient taken off study.

Aggressive supportive care improves outcome, particularly in high-risk patient populations receiving very intensive therapy as incorporated in this trial. The following guidelines are intended to give general direction for optimal patient care and to encourage uniformity in the treatment of this study population. General guidance may also be found in: Supportive Care of Children with Cancer: Current Therapy and Guidelines from the Children's Oncology Group, 2004 ed., Arnold J. Altman, M.D.

Hydration/Allopurinol/Rasburicase (recombinant urate oxidase)

All infants should be placed on allopurinol (250mg/m^2/day or 10 mg/kg/day divided into 3 divided doses orally or intravenously) or Rasburicase (recombinant urate oxidase) when the diagnosis of leukemia is made or strongly suspected. Prior to instituting Induction therapy, all patients should be well hydrated. Evidence of severe tumor lysis syndrome should be stabilized prior to the institution of therapy. In patients with extremely elevated WBC (> 300,000), exchange transfusion is strongly recommended.

Venous Access

Due to the need for frequent blood sampling, intensive chemotherapy, nutritional support and vesicant use, it is **essential** that all patients have a central venous catheter (preferably double lumen) placed. A central line (broviac catheter) is preferable to a portacath.

Blood Components

Blood products should be irradiated following the current FDA guidelines found at:
http://www.fda.gov/cber/gdlns/gamma.htm

Investigators in Canadian institutions need to follow the CSA standards for Blood and Blood Components CAN/CSA-Z902-04 issued in March 2004 and available at http://www.shopcsa.ca.

Red blood cells (RBCs)
Transfusion with RBCs is indicated to correct severe or symptomatic anemia or acute blood loss.

Platelets
Transfusion with platelets is indicated to correct bleeding manifestations and may be indicated for severe thrombocytopenia without bleeding particularly in the setting of an invasive procedure.

Nutrition

Protein-calorie malnutrition due to chemotherapy induced loss of appetite, nausea, vomiting, mucositis, and sepsis is a major concern. Aggressive nutritional support should be instituted when patient's weight/height ratio ÷ median weight/median height ratio for age and sex falls below 80% **or** when the serum albumin is less than 3 mg/dL.

Caution is advised with the use of early feeding / NG feeding in patients with difficult early courses or extensive mucositis/diaper area skin ulceration. NEC and intestinal perforation have been observed in such infants. Total parenteral nutrition (TPN) should be strongly considered in such infants until it is certain there is no risk to the gut.

Fever and Neutropenia
Aggressively manage episodes of fever (≥ 100.5ºF) particularly during Induction/Intensification or when the patient is neutropenic with an ANC ≤ 1000. The risk of life threatening infection is particularly high during the first 4-6 weeks of therapy or when patients are neutropenic with an ANC ≤ 1000. It is strongly advised that patients with fever and neutropenia (ANC < 1000) not be managed with an outpatient antibiotic regimen. It is mandatory that patients with an ANC < 500 and fever be hospitalized with immediate institution of broad spectrum IV antibiotics adjusted appropriately for the causative organism.

The specific choice of antibiotics to be used in empiric treatment of febrile neutropenia is dependent on your institution's experience regarding the type of infecting organisms, and antibiotic sensitivity. Adequate coverage for gram positive organisms including viridans streptococci in addition to double gram negative coverage should be strongly considered for patients admitted with fever and neutropenia.

In the absence of response after 3-5 days, institution of antifungal therapy should be strongly considered. Patients that require amphotericin should receive a lipid formulation to decrease amphotericin associated toxicity. These infants are also at high risk for life-threatening viral infections, particularly RSV (see RSV Prophylaxis and Treatment sections below), during respiratory season.

Infection Prophylaxis and Treatment
Bacterial and fungal infections have been prevalent and often severe during Induction on AALL0631. As shown in Table 1, there have been 4 fatal infections in the first 26 patients. The following tables summarize the Grade 3 or greater infectious toxicities that have been reported during the Induction phase of therapy on AALL0631. Of the 4 gram negative bacteremias, it is noteworthy that 2 were breakthrough infections, occurring 5 and 7 days after starting broad spectrum antibiotics.

All Infections

Organism Type	AE's	Fatal AE's	% of AE's	# Patients	% of Patients
Bacteria	19	2	76%	15	58%
Fungi	4	2	16%	4	15%
Viral	2	0	8%	2	8%
Totals	25	4	100%	18*	69%*

* these are not simple sums, since some patients had multiple AE's

Bacterial Infections

Site/type of bacterial infection	AE's	Fatal AE's	% of AE's	# Patients	% of patients
Bloodstream	16	2	64%	13	50%
Gram positive	12	1	48%	12	46%
Gram negative	4	1	16%	4	15%
Urine	3	0	12%	2	8%
Gram positive	1	0	4%	1	4%
Gram negative	2	0	8%	2	8%

Bacterial Blood Isolates

Organism Name	N
Gram Positive	**12**
Bacillus NOS	2 (1*)
Enterococcus faecalis	1
Staphylococcus NOS	1
Staphylococcus epidermidis	1
Streptococcus pneumoniae	1
Streptococcus mitis	3
Viridans group *Streptococcus*	3
Gram Negative	**4**
Enterobacter cloacae	1
Escherichia coli	2
Pseudomomas aeruginosa	1*

* fatal infections

Fungal Infections

Isolate	Site	Fatal?	Comments
Candida albicans	Blood	N	
Candida tropicalis	Blood	Y	
Aspergillus fumigatus	Nasal sinsuses/ brain	Y	
Aspergillus fumigatus	Lung	N	Found incidentally at autopsy in patient that died of Pseudomonal sepsis

Based on these data, we will emphasize our strong recommendation that patients should be hospitalized during Induction therapy until there is evidence of marrow recovery, and that all potential bacterial infections be treated promptly with empiric antibiotic therapy with broad coverage for BOTH gram positive and gram negative organisms. As the predominant pathogenic bacteria are gram positive organisms including viridians streptococci, the empiric gram positive coverage should include vancomycin, clindamycin or a drug appropriate for the treatment of viridians streptococci.

Intravenous Immunoglobulin

All patients are to receive intravenous immunoglobulin at a dose of 400 mg/kg if serum IgG level is below 500 mg/dL. Doses should be repeated every 4 weeks as needed to keep IgG level at 500 mg/dL or greater.

Antibiotic Prophylaxis

Infection related mortality continues to be high during Induction/Intensification. There are insufficient data to support specific recommendations regarding the use of antibiotic prophylaxis.

Pneumocystis Prophylaxis

PCP prophylaxis should be started as soon as possible after the diagnosis of ALL is confirmed and continued until 6 months after all therapy is completed.

1. The drug of choice is trimethoprim-sulfamethoxazole at a dosage of 150/750 mg/m^2/day in 2 divided doses on 3 consecutive days per week in **infants ≥ 2 months of age**.
    a. Trimethoprim-sulfamethoxazole must be held on the days of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 μM.
2. Second line options include:
    a. Dapsone 2 mg/kg/day in **infants ≥ 1 month of age**, or
    b. Aerosolized pentamidine for **all age infants**.

Fungal Prophylaxis

Azole antifungal agents (i.e., fluconazole, itraconazole, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity. Investigator caution is advised if azole antifungals are used.

Azole antifungals may also increase the levels of lestaurtinib if taken concurrently. For those patients receiving lestaurtinib, azole antifungals are discouraged beginning Week 8 of therapy. Fungal prophylaxis with azoles is permissible in Consolidation and Continuation EXCEPT during the weeks where lestaurtinib is given. A 4-day azole "washout" period prior to beginning lestaurtinib is recommended to minimize the risks of drug interactions.

The incidence of fungal infections is relatively high during Induction treatment (4/26 patients; 15%). Although the confidence interval around the 15% point estimate is wide (6 to 34%), at this level it is reasonable to consider antifungal prophylaxis and/or structured empirical antinfungal therapy. An alternative strategy is to use empirical antifungal therapy in neutropenic patients on or after 3-5 days of persistent fever or recurrent fever receiving broad spectrum antibiotics. Amphotericin B, liposomal amphotericin B, and caspofungin are licensed for this indication. The strategy for empricial antifungal therapy is to provide early treatment for clinically occult mycoses and prophylaxis in high risk neutropenic patients. Micafungin is licensed for prophylaxis during neutropenic phase in adult HSCT patients. Although not licensed for use in pediatric patients, micafungin has been extensively studied in the neonatal population. Pharmacokinetic and bridging pharmacodynamic studies have defined dosages of micafungin that would be active in treatment of invasive candidiasis, as well as for prophylaxis in this population.

There are downsides to all agents for fungal prophylaxis in this age range. Only two agents are approved and have dosing data and extensive experience with use in infants of all ages: fluconazole and amphotericin. There are empiric data that fluconazole is an effective prophylactic treatment strategy for adults undergoing SCT, and perhaps for adults with acute leukemia in Induction therapy.[72] There are no clear data on the efficacy of fluconazole for prophylaxis of fungal infections in pediatric patients with leukemia. It is well-tolerated in infants, but there are significant theoretical concerns about how this agent might affect the metabolism of chemotherapy agents in infants, particularly vincristine. If it is used, careful attention should be paid to vincristine toxicity. There are no empiric data to establish that amphotericin is a good agent for prophylactic use, and there are significant concerns about renal toxicity with amphotericin in this patient population. Caspofungin is approved for use in infants 3 months of age and older and there are some dosing data in younger infants. However, there are, at this time, no empiric data that caspofungin is an effective strategy for anti-fungal prophylaxis during leukemia Induction therapy. There are significant limitations for all the other agents, including lack of dosing information (most of the agents) and potential hepatic toxicity (voriconazole and posaconazole). It is also important to note that the concerns regarding inhibition of the metabolism of chemotherapy agents (particularly vincristine) are greater for voriconazole and posaconazole than they are for fluconazole. In addition, micafungin has recently received a pediatric warning label because of the occurrence of liver tumors in rats. The clinical significance of these findings for micafungin and other members of this class is

uncertain. However, given this data micafungin should only be considered if other antifungals are not appropriate. Local centers should consider all of these data carefully when making clinical decisions regarding fungal prophylaxis in patients enrolled on this study. There are pluses and minuses with each prophylactic choice, for example coverage of specific organisms and tissue penetration (such as CNS). If prophylaxis is utilized, consultation with Infectious Disease is strongly recommended.

RSV Prophylaxis

Palivizumab 15 mg/kg IM every month should be initiated just before the onset of the RSV season and terminated at the end of the RSV season.

RSV Treatment

All RSV infections (upper and lower respiratory) should be treated. Ribavirin 6 grams diluted in 300 mL preservative-free sterile water (20 mg/mL) over 12-18 hours by aerosol through a SPAG-2 unit should be administered every day for a minimum of 3-7 days. Alternatively, in the non-ventilated patient, ribavirin 2 grams may be administered over 2 hours 3 times per day for a minimum of 3-7 days. The 6 grams of ribavirin delivered in the 3 times per day dosing should be diluted in 100 mL of preservative-free sterile water to a final concentration of 60 mg/mL.

1. Additionally, palivizumab 15 mg/kg IM should be administered, if not already given as prophylaxis.

Influenza Immunization

Infants $\geq$ 6 months of age should receive the influenza immunization with the trivalent inactivated influenza vaccine (TIV). Household contacts and out-of-home caregivers should also receive the influenza immunization with TIV.

Varicella Infection and Prophylaxis

Varicella infection occurred in 7 of the 115 patients enrolled on CCG 1953. Of these 4 (57%) had at least 1 recurrence. Patients should be treated promptly with intravenous acyclovir, and monitored closely for the development of invasive systemic disease. The use of oral acyclovir for prophylaxis is recommended after completion of treatment for varicella.

Empiric Management of Pulmonary Infiltrates

Pulmonary infiltrates should be evaluated in the context of the patient's clinical and laboratory profile. If the patient is not neutropenic, and the pulmonary lesions on CT scan are not particularly suggestive of a mold infection (Aspergillus, mucor), consider coverage with broad spectrum antibiotics and evaluate for viral causes of pulmonary infiltrates including RSV, influenza, and CMV. If the patient develops progressively worsening clinical or laboratory features or if the patient is neutropenic, more aggressive diagnostic measures should be undertaken. Empiric coverage should consider gram-negative and positive bacteria, fungi, RSV, influenza, CMV, Pneumocystis, and Legionella. Begin empiric treatment with amphotericin B given the high likelihood of fungal disease during Induction and after the use of steroids. It is advisable to seek an infectious disease consult under these circumstances.

Stress Steroid Support

If serious illness (particularly a potentially life-threatening infection) should occur in close proximity to the completion of the Induction or Re-Induction, consider additional "stress steroid" support.

Mucositis
Moderate (Grade 3) or severe (Grade 4) mucositis requires vigorous treatment including IV fluids, hyperalimentation, and strong consideration of broad spectrum antibiotics if febrile or ill appearing. Antifungal and antiviral therapy should be considered based on culture results and clinical evaluation. Daily oral antifungal prophylaxis with fluconazole should be strongly considered in patients not receiving lestaurtinib. DO NOT PROCEED WITH FURTHER HD MTX/DAUNORUBICIN UNTIL MUCOSITIS BEGINS TO HEAL.

Perineal Irritation
There is a high risk of Grade 3-4 diaper area skin ulceration with daunorubicin and HD MTX. **Placement of a foley catheter for 48-72 hours during administration/urinary excretion of these drugs has dramatically reduced this diaper area skin ulceration**. Use of a strong barrier technique is also recommended, such as Critiq-aid. If unable to place a foley catheter, frequent diaper changes are advised during HD MTX/daunorubicin administration. If severe skin ulceration occurs, manage skin care aggressively and strongly consider antibiotic coverage until skin heals. DO NOT PROCEED WITH FURTHER HD MTX/DAUNORUBICIN UNTIL SKIN BEGINS TO HEAL.

Antiemetic Protection
Antiemetics should be given as needed. The routine use of steroids is discouraged. Administer lestaurtinib with food to decrease treatment associated nausea and vomiting, and consider administering a 5-HT_3 antagonist with lestaurtinib doses to prevent nausea and vomiting.

Expanded Supportive Care Data Collection
Given the risks of serious infections that have prompted the changes to Induction chemotherapy, centers are required to report via eRDE detailed information regarding infections and supportive care measures so that we can carefully assess the impact of the protocol changes. The Induction reporting period case report form has been modified to gather information regarding use of antifungal prophylaxis and empiric treatment, IgG levels and use of IVIG, and duration of hospitalization during Induction.

APPENDIX II: CYP3A4/5 INHIBITORS AND INDUCERS

Note: Anticonvulsants should definitely be avoided. The use of the other agents listed below should be limited due to concerns of drug interactions.

Adapted from Cytochrome P-450 Enzymes and Drug Metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th edition. Hudson, OH; LexiComp Inc. 2000: 1364-1371.

CYP3A4/5 Inhibitors:		CYP3A4/5 Inducers:
Amiodarone	Nevirapine	Carbamazepine
Anastrozole	Norfloxacin	Dexamethasone
Azithromycin	Norfluoxetine	Ethosuximide
Cannabinoids	Omeprazole (weak)	Glucocorticoids (except as
Cimetidine	Oxiconazole	prescribed in treatment
Clarithromycin	Paroxetine (weak)	regimen)
Clotrimazole	Posaconazole	Griseofulvin
Cyclosporine	Propoxyphene	Modafinil
Danazol	Quinidine	Nafcillin
Delaviridine	Quinine	Nelfinavir
Diethyldithiocarbamate	Quinupristin and dalfopristin	Nevirapine
Diltiazem	Ranitidine	Oxcarbazepine
Dirithromycin	Ritonavir	Phenobarbital
Disulfiram	Roxithromycin	Phenylbutazone
Entacapone (high dose)	Saquinavir	Phenytoin
Erythromycin	Sertindole	Primidone
Ethinyl estradiol	Sertraline	Progesterone
Fluconazole (weak)	Telithromycin	Rifabutin
Fluoxetine	Troleandomycin	Rifapentine
Fluvoxamine	Valproic acid (weak)	Rifampin
Gestodene	Voriconazole	Rofecoxib (mild)
Grapefruit juice	Verapamil	St. John's Wort
Indinavir	Zafirlukast	Sulfadimidine
Isoniazid	Zileuton	Sulfinpyrazone
Itraconazole		Troglitazone
Ketoconazole		
Metronidazole		
Mibefradil		
Miconazole (moderate)		
Nefazodone		
Nelfinavir		

This list may not be comprehensive due to new agents coming to market. Below is a link to a list of drugs that are metabolized by cytochrome P450 isoform. Drug names are hyperlinks to specific literature references, most of which include a link to the abstract of the article in the NLM's PubMed database.

http://medicine.iupui.edu/flockhart/

APPENDIX III: P-GLYCOPROTEIN SUBSTRATES/INDUCERS (OVER TIME)/INHIBITORS

P-GLYCOPROTEIN SUBSTRATES	P-GLYCOPROTEIN INHIBITORS	P-GLYCOPROTEIN INDUCERS
amiodarone	amiodarone	aspirin
amprenavir	amitriptyline	dexamethasone
(also indinavir, fosamprenavir,	(also desipramine, imipramine, trimipramine)	doxorubicin
ritonavir, saquinavir, nelfinavir)	atorvastatin (also lovastatin, simvastatin)	nefazodone
atorvastatin, lovastatin	azelastine	prazosin
celiprolol	carvedilol, propranolol	rifampin
cetrizine	chlorpromazine, prochlorperazine	St. John's Wort
cimetidine	cimetidine, ranitidine	trazodone
ciprofloxacin	clarithromycin, erythromycin	vinblastine
colchicines	cyclosporine	
cyclosporine	dexrazoxane	
daunorubicin	diltiazem, felodipine	
(also doxorubicin, idarubicin)	(also nicardipine, nifedipine, nitredipine,	
desloratidine, loratadine	verapamil)	
dexamethasone	dipyridamole,	
digitoxin, digoxin	disulfiram	
diltiazem	doxepin	
docetaxel	esomeprazole (also lansoprazole, omperazole)	
erythromycin	fluphenazine	
estradiol	grapefruit juice	
etoposide, teniposide	haloperidol	
fexofenadine	hydrocortisone	
hydrocortisone	hydroxyzine	
imatinib	imatinib	
irinotecan	itraconazole, ketoconazole	
ivermectin	ivermectin	
lidocaine	lidocaine	
loperamide	maprotiline	
methotrexate	mefloquine	
mitomycin	midazolam	
nadolol	mifepristone	
nicardipine	mitomycin	
ondansetron	nefazodone	
paclitaxel	nelfinavir	
pravastatin	(also ritonavir, saquinavir)	
quinidine	ofloxacin	
ranitidine	probenicid	
rifampin	progesterone	
sirolimus	propafenone	
tacrolimus	quinidine, quinine	
verapamil	reserpine	
vinblastine, vincristine	rifampin	
	tracrolimus	
	tamoxifen	
	testosterone	
	vinblastine	

Table adapted from Lexi-Comp's Drug Interaction Handbook 2nd edition 2004

Note: Predictions of drug interactions due to an effect on PGP transport is limited by the fact that drugs may be metabolized by multiple pathways, offering an alternative elimination route; the sum of the multiple drug effects on PGP is unknown; and PGP activity is influenced by non-drug entities such as: inflammation, irradiation, etc.)

APPENDIX IV: Instructions to Patient/Caregiver for Administering Lestaurtinib (CEP-701) at a 5 mg/mL dilution

This document has instructions for patients/caregivers on the preparation, administration and storage of Lestaurtinib solution. Below are instructions on how to prepare a mixture of Lestaurtinib and juice, how to give your child the Lestaurtinib/juice mixture, and how to store the drug and supplies. You should read and learn the information on these pages before you prepare and give your child the Lestaurtinib/juice solution. **Please read these instructions carefully and ask you doctor or pharmacist any questions you may have.**

The following are instructions for storing Lestaurtinib:

1. The Lestaurtinib solution should be stored in its bottle at room temperature of 20 to 25°C (68–77°F) in the box it came in. (**NOTE**: for centers outside the US, solutions of Lestaurtinib in juice should be stored below 25ºC (77°F))
2. The Lestaurtinib solution should not be exposed to light. Keep used and unused bottles in the original boxes they came in.
3. Lestaurtinib must be kept out of reach of children.
4. Any used and unused bottles of Lestaurtinib should be returned in the boxes they came in to the investigator at each study visit.

The following are general instructions on giving Lestaurtinib to your child:

1. Lestaurtinib is to be given orally (by mouth) only.
2. Give your child the Lestaurtinib/juice mixture approximately every 12 hours (there must be at least 8 hours between doses).
3. Lestaurtinib can be given with food to reduce the amount of nausea and vomiting the drug may cause.
4. If your child's study doctor prescribed medicine to prevent nausea or vomiting with Lestaurtinib, you should give your child this medicine 30-60 minutes before you give the Lestaurtinib/juice mixture.
5. If your child vomits after you've given a dose of the Lestaurtinib/juice mixture, do not repeat this dose. Give your child the next dose at the next scheduled time.
6. Juices approved for use in mixing with Lestaurtinib are apple, grape, pineapple, V8® 100% vegetable juice, cranberry and orange juice.

Instructions for preparing the Lestaurtinib/juice solution (mixture)

You will need the following items to prepare the Lestaurtinib/juice solution:

- ❑ 100 mL Bottle of Lestaurtinib drug and the box it came in.
- ❑ Push-in bottle adapter.
- ❑ One 5 mL oral syringe.
- ❑ Two 10 mL oral syringes (or one 10 mL and one 5 mL oral syringe depending on your child's dose).
- ❑ Apple juice or any type of juice approved for mixing with Lestaurtinib (see above).
- ❑ Medicine cup or other container for mixing the drug and juice.

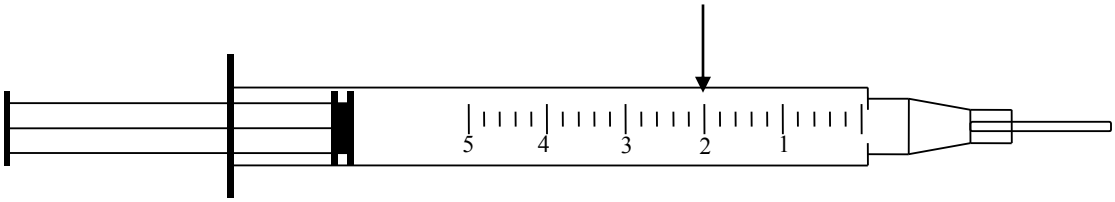
1. Remove the child-resistant cap from the 100 mL bottle of Lestaurtinib.

2. Insert the push-in adapter into the top of the 100 mL bottle of Lestaurtinib (if not already done).

3. Remove the cap from the 5 mL oral syringe and insert the tip into the push-in adapter.

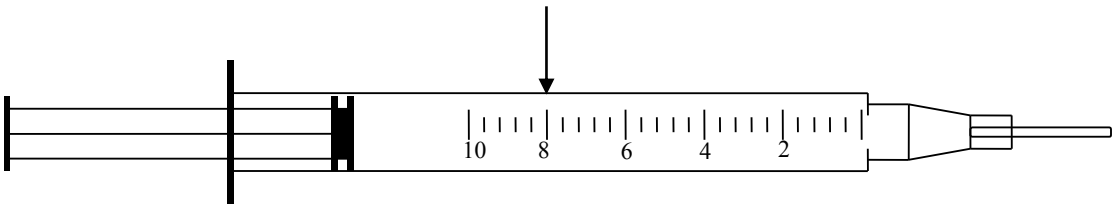
4. Flip the 100 mL bottle of Lestaurtinib with the connected 5 mL oral syringe so that the bottle is upside down and the tip of the syringe is facing upwards.

5. Gently pull down on the plunger of the syringe and pull 2 mL of the Lestaurtinib liquid into the syringe. There should be liquid visible in the top portion of the syringe up to the '2' mark on the syringe (see the diagram below).



6. Pull the syringe (now filled with the 2 mL of Lestuartinib liquid) out of the push-in adapter. Leave the push-in adapter in the bottle, replace the child-resistant cap and twist it to lock the cap onto the bottle. (If the cap doesn't lock, remove it and repeat this step. Make sure the cap and bottle are clean of any Lestaurtinib solution.)

7. Take the 10 mL oral syringe and withdraw 8 mL of apple juice, or any other approved juice, into this syringe (see diagram below).



8. Slowly empty the juice from the syringe into the medicine cup or mixing container by pushing forward on the syringe.

9. Take the syringe with the 2 mL of Lestaurtinib liquid you withdrew in step #5 and slowly empty the liquid into the same container with the juice.

10. Using a plastic spoon, gently mix or stir the Lestaurtinib liquid and the juice for at least one minute, or until they are well mixed.

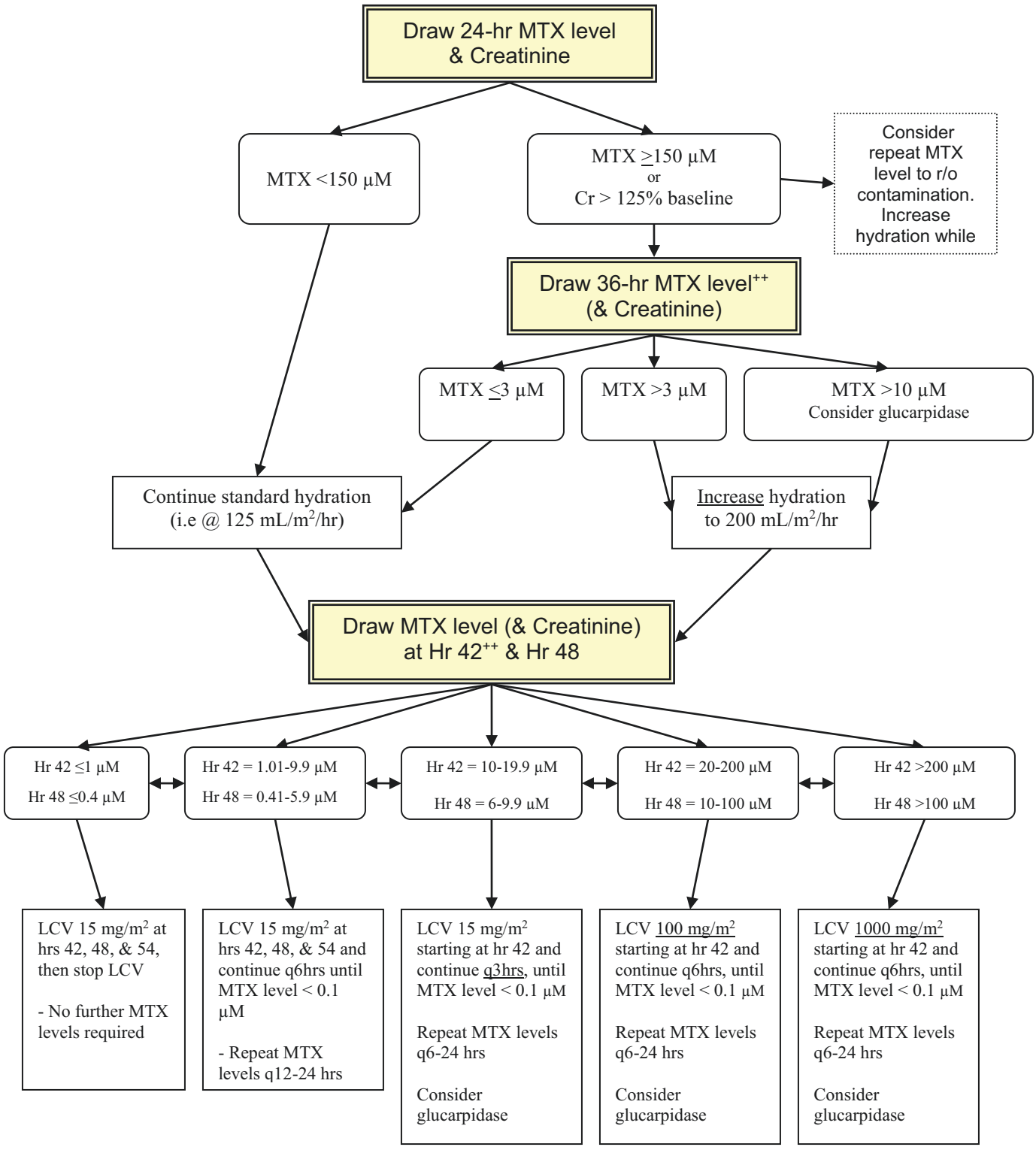
11. You now have a solution with a 5mg/mL concentration of Lestaurtinib. **Your doctor will tell you how much of this solution you should be giving your child.** Take the second (unused) 10 mL or 5 mL oral syringe and withdraw the amount of the Lestaurtinib/juice mixture your doctor instructed you to from the mixing container. Give your child this dose of the Lestaurtinib/juice mixture. If you are administering this solution by nasogastric (NG) tube, then after giving your child the Lestaurtinb/juice mixture, give him/her a 2nd syringe of juice only (no medication) followed by a flush of the NG tube with 10 – 20 mL of juice or water to make sure your child got all of the medicine.

12. Give your child the diluted solution immediately after mixing. (If the solution of Lestaurtinib in juice must be stored, it may be kept one hour at room temperature or up to 8 hours refrigerated. It should be protected from light during the time it is stored.)

13. After you have given your child the Lestaurtinib/juice mixture, pull the plungers out of all the syringes and rinse the syringes, plungers and medicine cups with warm water for 30 seconds. Place the plungers back into their syringes and store them and the mixing cups in the original boxes they came in for the next time.

APPENDIX V: HIGH DOSE METHOTREXATE FLOW CHART

(Please refer to Section 5.8 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.

APPENDIX VI: MERCAPTOPURINE DOSING GUIDELINES

MERCAPTOPURINE 75 mg/m²

Body Surface Area (m²)*	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 - 1.00	1½ tab / day	525 mg/wk

*****Patients exceeding a BSA of 1.00 m² should have their MP doses calculated on actual BSA with no maximum dose.*

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