Activated: August 9, 2010
Closed: March 21, 2018
Version Date: 10/26/17
Amendment #5A

CHILDREN'S ONCOLOGY GROUP

AALL0932

Treatment of Patients with Newly Diagnosed Standard Risk B-Lymphoblastic Leukemia (B-ALL) or Localized B-lineage Lymphoblastic Lymphoma (B-LLy)

A Groupwide Phase III Study

STUDY CHAIR

[redacted]

TABLE OF CONTENTS

SECTION			PAGE
STUDY COMMITTEE			5
ABSTRACT			8
EXPERIMENTAL DESIGN SCHEMA (B-ALL PATIENTS): FOR PATIENTS ENROLLED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET			10
EXPERIMENTAL DESIGN SCHEMA (B-ALL PATIENTS): FOR PATIENTS ENROLLED AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET			11
EXPERIMENTAL DESIGN SCHEMA (B-LLY AND DS B-LLY PATIENTS)			12
1.0	GOALS AND OBJECTIVES (SCIENTIFIC AIMS)		13
	1.1	Primary Objectives	13
	1.2	Secondary Objectives	13
	1.3	Exploratory Objectives	14
2.0	BACKGROUND		14
	2.1	Rationale for Selected Approach and Trial Design for B-ALL	14
	2.2	Rationale for Selected Approach and Trial Design for Patients with B-LLy	21
	2.3	Development Plans	23
	2.4	Patient Enrollment After AR B-ALL Accrual Goals Have Been Met	24
	2.5	Rationale for additional IT therapy for Non-Down Syndrome (Non-DS) B-Acute Lymphoblastic Leukemia (B-ALL) Patients with Central Nervous System 2 (CNS2) Disease (Amendment # 4)	24
3.0	STUDY ENROLLMENT AND PATIENT ELIGIBILITY		26
	3.1	Study Enrollment	26
	3.2	Patient Eligibility Criteria	30
	3.3	Definitions	32
4.0	TREATMENT PLAN		37
	4.1	Overview of Treatment Plan	37
	4.2	Induction (35 days) – B-ALL and B-LLy Patients	42
	4.3	Consolidation (28 days) – AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C and B-LLy Patients	48
	4.4	Interim Maintenance I (56 days) – AR B-ALL Patients, LR Patients Randomized to Arm LR-C, and B-LLy Patients	52
	4.5	Delayed Intensification (56 days) - AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C, and B-LLy Patients	55
	4.6	Interim Maintenance II (56 days) – AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C, and B-LLy Patients	60
	4.7	Maintenance Arm A (AR B-ALL Patients)	64
	4.8	Maintenance Arm B (AR B-ALL Patients)	68
	4.9	Maintenance Arm C (AR B-ALL Patients and LR B-ALL Patients Randomized to Arm LR-C)	72
	4.10	Maintenance Arm D (AR B-ALL Patients)	76
	4.11	Maintenance Arm LLy (B-LLy Patients)	80
	4.12	Consolidation (19 Weeks) – LR B-ALL Patients Randomized to Arm LR-M	83
	4.13	Maintenance Arm LR-M – Cycle 1 (LR B-ALL Patients Randomized to Arm LR-M)	90
	4.14	Maintenance Arm LR-M – Cycle 2 (LR B-ALL Patients Randomized to Arm LR-M)	93
	4.15	Maintenance Arm LR-M – Cycle 3 (LR B-ALL Patients Randomized to Arm LR-M)	96

4.16 Maintenance Arm LR-M – Cycle 4 (LR B-ALL Patients Randomized to Arm LR-M) 99
4.17 Maintenance Arm LR-M – Cycle 5 (LR B-ALL Patients Randomized to Arm LR-M) 102
4.18 Maintenance Arm LR-M – Cycle 6 (LR B-ALL Patients Randomized to Arm LR-M) 105
4.19 Maintenance Arm LR-M – Cycle 7 (LR B-ALL Patients Randomized to Arm LR-M) 108
4.20 Induction (35 Days) – DS SR B-ALL and DS B-LLy Patients 111
4.21 Consolidation (28 days) –DS SR B-ALL and DS B-LLy Patients 115
4.22 Interim Maintenance I (56 days) - DS SR B-ALL and DS B-LLy Patients 118
4.23 Delayed Intensification (56 days) - DS SR B-ALL and DS B-LLy Patients 121
4.24 Interim Maintenance II (56 days) - DS SR B-ALL and DS B-LLy Patients 126
4.25 Maintenance Arm DS - DS SR B-ALL and DS B-LLy Patients 129

5.0 DOSE MODIFICATIONS FOR TOXICITIES 132
5.1 Asparaginase [E.coli, Pegaspargase (PEG-Asparaginase) or Erwinia] 132
5.2 Cyclophosphamide 133
5.3 Cytarabine (ARAC) IV 134
5.4 Intrathecal Cytarabine 134
5.5 Doxorubicin (Anthracyclines) 134
5.6 Intrathecal Methotrexate 135
5.7 IV Methotrexate 137
5.8 PO 6-Mercaptopurine (6-MP) - Consolidation 141
5.9 PO Methotrexate (MTX) and 6-Mercaptopurine (6-MP) – Maintenance for all Arms 143
5.10 Steroid (Dexamethasone) 147
5.11 PO 6-Thioguanine (6-TG) - Delayed Intensification: 147
5.12 Vincristine 148
5.13 Drug Interactions 149

6.0 DRUG INFORMATION 150

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED 151
7.1a Required and Optional Clinical, Laboratory and Disease Evaluations – AR B-ALL and LR B-ALL Randomized to Arm LR-C 151
7.1b Required and Optional Clinical, Laboratory and Disease Evaluations – LR B-ALL Randomized to Arm LR-M 152
7.1c Required and Optional Clinical, Laboratory and Disease Evaluations – DS SR B-ALL 153
7.1d Required and Optional Clinical, Laboratory and Disease Evaluations – B-LLy and DS-B-LLy 154
7.2 Studies Suggested to be Obtained After Stopping Therapy (B-ALL Patients) 155
7.3 Studies Suggested to be Obtained After Stopping Therapy (B-LLy Patients) 155
7.4 At Relapse 155
7.5 GEOGRAPHICAL SAMPLE DISTRIBUTION 156

8.0 SUPPORTIVE CARE GUIDELINES 157
8.1 General Guidelines 157
8.2 Guidelines for Induction 159
8.3 Patients with Down syndrome 160

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA 161
9.1 Criteria for Removal from Protocol Therapy for B-ALL and B-LLy Patients 161
9.2 Off Study Criteria (B-ALL and B-LLy Patients) 162

10.0 STATISTICAL CONSIDERATIONS 162
10.1 Statistical Design 162
10.2 Patient Accrual and Expected Duration of Trial 162

10.3 Statistical Analysis Methods 164
10.4 Gender and Minority Accrual Estimates 167

11.0 EVALUATION CRITERIA 168
11.1 Common Terminology Criteria for Adverse Events (CTCAE) 168
11.2 Response Criteria for Patients with Leukemia (B-ALL) 168
11.3 Response Criteria for Patients with B-LLy[95,96] 168

12.0 ADVERSE EVENT REPORTING REQUIREMENTS 169
12.1 Purpose 169
12.2 Determination of Reporting Requirements 169
12.3 Reporting of Adverse Events for Commercial Agents - via CTEP-AERS 170
12.4 Routine Adverse Event Reporting 170

13.0 RECORDS AND REPORTING 171
13.1 CDUS 171

14.0 PATHOLOGY GUIDELINES AND SPECIAL STUDIES FOR B-LLY PATIENTS 171
14.1 Pathology Goals 171
14.2 Requirements for Handling Tissue or Cytology Specimens at Primary Institutions 172
14.3 Immunophenotyping Recommendations for Primary Institutions 172
14.4 Pathology Staging Criteria 173
14.5 Retrospective Central Pathology Review 173
14.6 Optional Minimal Marrow Disease (MMD) Biology Studies 175
14.7 Optional Tissue Banking and Subsequent Biologic Studies 177
14.8 Preparation of Tissue Banking Samples at Time of Diagnosis or Relapse 177
14.9 Optional Studies of Genomic Variation 179

15.0 THE PATIENT LEUKEMIA EXPERIENCE ANCILLARY STUDY: 179
15.1 Correlative Study Design: 180
15.2 Specific Hypotheses 182
15.3 Specific Aims 183
15.4 Statistical Design 184
15.5 Significance 185

16.0 THE LEUKEMIA PHYSICAL FUNCTIONING STUDY: 186
16.1 Correlative Study Design: 186
16.2 Background and Specific Hypotheses 190
16.3 Statistical Design 194
16.4 Significance 195

APPENDIX I: MERCAPTOPURINE DOSING GUIDELINES 197

APPENDIX II: THIOGUANINE DOSING GUIDELINES 199

APPENDIX III: MERCAPTOPURINE DOSING GUIDELINES 201

APPENDIX IV: YOUTH INFORMATION SHEETS 203

APPENDIX V: STAGING CLASSIFICATION OF CHILDHOOD NON-HODGKIN LYMPHOMA 207

APPENDIX VI: CTEP REGISTRATION PROCEDURES 210

APPENDIX VII: POSSIBLE DRUG INTERACTIONS 211

REFERENCES: 215

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

AGENT	NSC#	IND#
6-Mercaptopurine	755	Exempt
Cytarabine	63878	Exempt
Cyclophosphamide	26271	Exempt
Doxorubicin	123127	Exempt
Dexamethasone	34521	Exempt
Erwinia Asparaginase	106977	Exempt
Methotrexate	740	Exempt
PEG L-Asparaginase	624239	Exempt
Vincristine Sulfate	67574	Exempt
Leucovorin Calcium	003590	Exempt
6-Thioguanine	000752	Exempt

ABSTRACT

The survival of children with newly diagnosed B-lymphoblastic leukemia (B-ALL) and B-lymphoblastic lymphoma (B-LLy) has markedly improved over the past 4 decades with cure rates now 80% - 85%. This has been achieved through the identification of effective combination chemotherapy, central nervous system (CNS) prophylaxis, and intensified post-Induction therapy that is very similar for B-ALL and B-LLy patients. For B-ALL the introduction of risk stratification, based on the risk of treatment failure, is used to modulate treatment intensity. The previous classification protocol AALL03B1 used by COG identified 4 distinct groups of standard risk B-ALL with different outcomes. The National Cancer Institute (NCI) Standard Risk group (> 365 days and < 10 years of age with an initial white blood cell count < 50 000/μL) was divided into Standard Risk low (SR-Low), Standard Risk Average (SR-Avg), Standard Risk High (SR-High) and Very High Risk (VHR) subgroups. A revised risk stratification system was implemented in 2010 when the second generation of frontline COG ALL trials opened to accrual, including this trial. The new classification study, AALL08B1, will continue to stratify B-ALL patients based on the combination of NCI risk group, sentinel cytogenetic lesions, clinical variables (CNS and testicular disease status) and early treatment response. Day 8 and 15 bone marrow (BM) morphology will no longer be used to assess early response and will be replaced by minimal residual disease (MRD) in peripheral blood (PB) at Day 8 and BM at Day 29 of Induction therapy. Based on these findings, B-ALL patients will be stratified into 1 of 4 risk groups for post-Induction therapy: Low Risk (LR), Average Risk (AR), High Risk (HR), and Very High Risk (VHR) with projected 5 year EFS rates of greater than 95%, 90% - 95%, 88% - 90% and less than 80%, respectively. All NCI SR B-ALL patients without central nervous system or testicular disease will be eligible to receive Induction on AALL0932. The LR and AR risk groups which are a subset of the NCI SR group, represent the patient population eligible to receive post-Induction therapy on AALL0932. Standard risk patients with Down syndrome (DS) and Day 29 BM MRD < 0.01% will also be eligible to receive post-Induction therapy on AALL0932 on a special stratum that will not include randomized questions. In addition, patients with localized (Murphy Stage I and II) B-LLy (without Down syndrome, CNS or testicular disease) from 1 - 30 years of age will be enrolled on a separate stratum and receive the same common Induction therapy given to B-ALL patients, followed by post-Induction therapy similar to the standard arm of the AR B-ALL group without any randomized questions in order to provide standardized treatment for children with B-LLy. Down syndrome B-LLy (DS B-LLy) patients will receive a modified Induction and post-Induction therapy same as for patients with DS SR B-ALL.

AALL0932 will explore the delivery of Maintenance therapy for children with AR B-ALL. This study will compare 2 different doses of methotrexate during Maintenance administered with and without a reduced frequency of vincristine/dexamethasone (VCR/DEX) pulses, every 12 weeks compared to every 4 weeks, respectively, in a 2 x 2 design. Average Risk B-ALL patients will be randomized to 1 of 4 Maintenance regimens: **(A):** VCR/DEX pulses at 4 week intervals and oral methotrexate at 20 mg/m²/week (standard arm); **(B):** VCR/DEX pulses at 4 week intervals and oral methotrexate at 40 mg/m²/week; **(C):** VCR/DEX pulses at 12 week intervals and oral methotrexate at 20 mg/m²/week**;** and **(D):** VCR/DEX pulses at 12 week intervals and oral methotrexate at 40 mg/m²/week. Patients on all arms will receive intrathecal methotrexate

every 12 weeks during Maintenance and the duration of therapy will continue to be gender-based. **During the first quarter of 2017, the Data and Safety Monitoring Committee (DSMC) released data that a futility boundary was crossed and that the study would not be able to demonstrate that 40 mg/m²/week of methotrexate is superior to 20 mg/m²/week of methotrexate. With Amendment #5, and effective January 13, 2017, the study committee recommended that all patients randomized to receive 40 mg/m²/week of methotrexate (Arms B and D) during maintenance have their dose lowered to 20 mg/m²/week, the standard of care therapy, even if they are tolerating higher doses. Subsequently, patients should have their doses of 6 mercaptopurine and methotrexate adjusted based on tolerability following normal dose escalation procedures, as outlined in the protocol Section 5.9.**

AALL0932 also seeks to confirm that children with LR B-ALL can obtain outstanding outcomes using either a P9904 based regimen that includes 6 courses of intermediate dose (1 g/m^2 over 24 hours) methotrexate without alkylating agents or anthracyclines (Arm LR-M), or one identical to that of AR patients receiving regimen C Maintenance as above (Arm LR-C). Low-risk patients will be randomized between these 2 treatments arms. The goal will not be to prove superiority of 1 regimen, but rather to determine if excellent outcomes (at least 95% five-year disease-free survival) are obtained. If both regimens meet this benchmark, then physicians and families can select the treatment that they prefer for low risk patients in the future. Another important goal of this study is to provide safe and standardized therapy to DS patients with SR B-ALL and DS B-LLy, and to facilitate further study of this biologically and clinically unique subgroup.

This trial will also incorporate prospective, standardized assessments of health related quality of life (HRQOL) among children with AR B-ALL using performance-based and parent-reported measurements. These data will serve as the basis for future screening and intervention strategies to minimize the morbidity of ALL and its therapy in the growing proportion of children with ALL that are cured. **UPDATE: Enrollment to both ancillary QOL studies is closed because accrual goals have been met.**

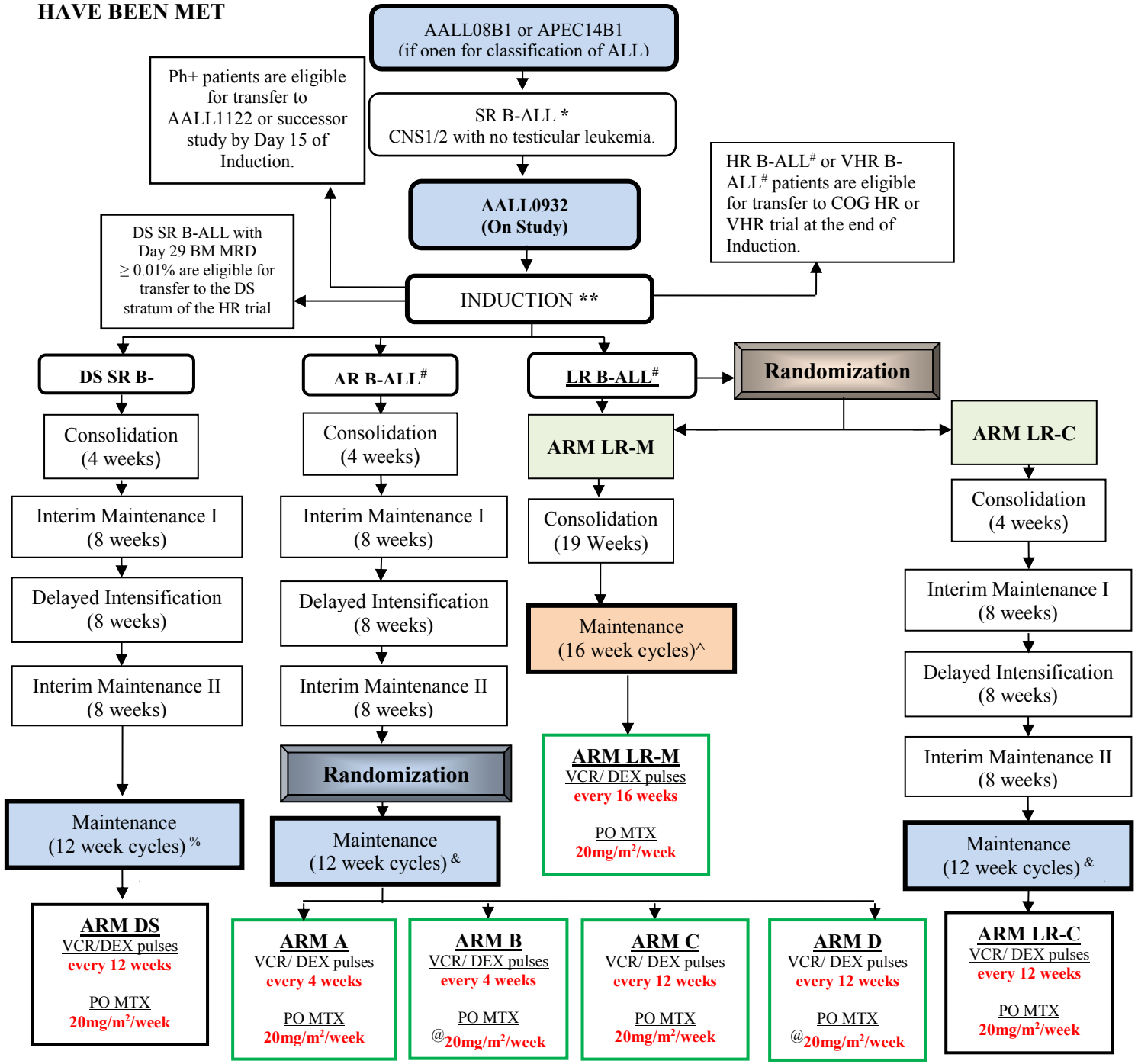
For patients with B-LLy, minimal marrow disease (MMD) and recurrent cytogenetic abnormalities by FISH at diagnosis will be studied to improve the understanding of the biology of localized B-LLy. Closed effective Amendent #5.

As of Amendment 3A, accrual goals for the Average Risk (AR) B-ALL cohorts have been met, therefore AR and Low Risk (LR) B-ALL patients will no longer receive post-Induction treatment on AALL0932. These patients will still be able to receive Induction treatment and risk stratification on AALL0932. Upon completion of Induction, AR and LR patients will come off protocol therapy. HR patients may be eligible for enrollment onto AALL1131 after Induction. There are no changes to enrollment for DS, B-LLy, or DS B-LLy patients. AR and LR B-ALL patients enrolled before accrual goals for AR patients have been met will continue to receive Post-Induction treatment on AALL0932.

Given the significantly inferior EFS reported for non-DS B-ALL patients with CNS2 disease treated on AALL0331 and AALL0232 and the available safety data on the use of more frequent IT therapy during Induction, with Amendment 4, we are modifying Induction on AALL0932 for patients with CNS2 disease such that they will receive twice weekly intrathecal therapy during Induction until 3 consecutive CSF samples after diagnosis are clear of blasts.

In addition to the change in maintenance methotrexate dosing for AR patients, Amendment #5 includes details regarding the planned transition from AALL08B1, *Classification of Newly Diagnosed Acute Lymphoblastic Leukemia* (ALL) to APEC14B1 (*Project:EveryChild, A Registry, Eligibility Screening, Biology and Outcome Study)* for B-ALL patients, and the discontinuation of MMD testing for B-LLy patients.

EXPERIMENTAL DESIGN SCHEMA (B-ALL Patients): FOR PATIENTS ENROLLED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET



* NCI/Rome Criteria
** Induction Therapy – 4 weeks/ 3 drugs.
Note: Leucovorin rescue will be given after each IT MTX for patients with Down syndrome during all applicable phases of therapy EXCEPT Maintenance.
Classification study AALL08B1 criteria (see Section 3.3 for further details)

DS SR B-ALL: Day 29 BM MRD < 0.01%
AR B-ALL: (a) No favorable cytogenetics, CNS1 or 2, Day 8 PB MRD < 1% & Day 29 BM MRD < 0.01%; (b) favorable cytogenetics, Day 29 BM MRD < 0.01%; and either Day 8 PB MRD ≥ 0.01% or CNS2.
LR B-ALL: Favorable cytogenetics, CNS1, Day 8 PB & Day 29 BM MRD < 0.01%

Favorable cytogenetics: *ETV6/RUNX1* (*TEL/AML1*) fusion or double trisomy of chromosomes 4 and 10

%Timed from the start of Interim Maintenance I for a total of 2 years for both girls and boys.

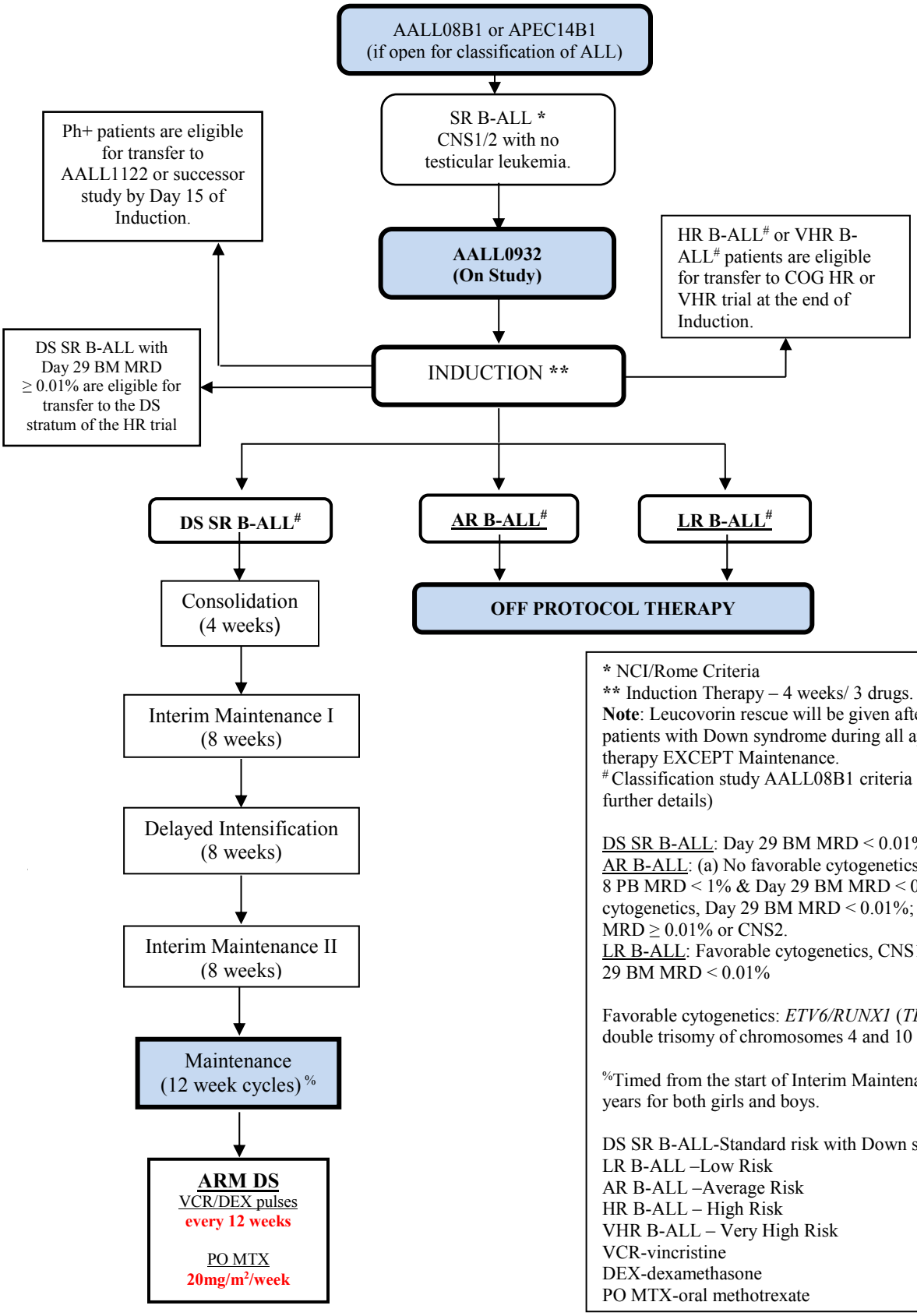
&Timed from the start of Interim Maintenance I for a total of 2 years for girls, and 3 years for boys.

^Timed from the date of diagnosis for a total of 2½ years

@Effective 01/13/17, reduce oral methotrexate from 40 mg/m²/week to 20 mg/m²/week

DS SR B-ALL-Standard risk with Down syndrome
LR B-ALL –Low Risk
AR B-ALL –Average Risk
HR B-ALL – High Risk
VHR B-ALL – Very High Risk
VCR-vincristine
DEX-dexamethasone
PO MTX-oral methotrexate

EXPERIMENTAL DESIGN SCHEMA (B-ALL Patients): FOR PATIENTS ENROLLED AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET



* NCI/Rome Criteria
** Induction Therapy – 4 weeks/ 3 drugs.
Note: Leucovorin rescue will be given after each IT MTX for patients with Down syndrome during all applicable phases of therapy EXCEPT Maintenance.
Classification study AALL08B1 criteria (see Section 3.3 for further details)

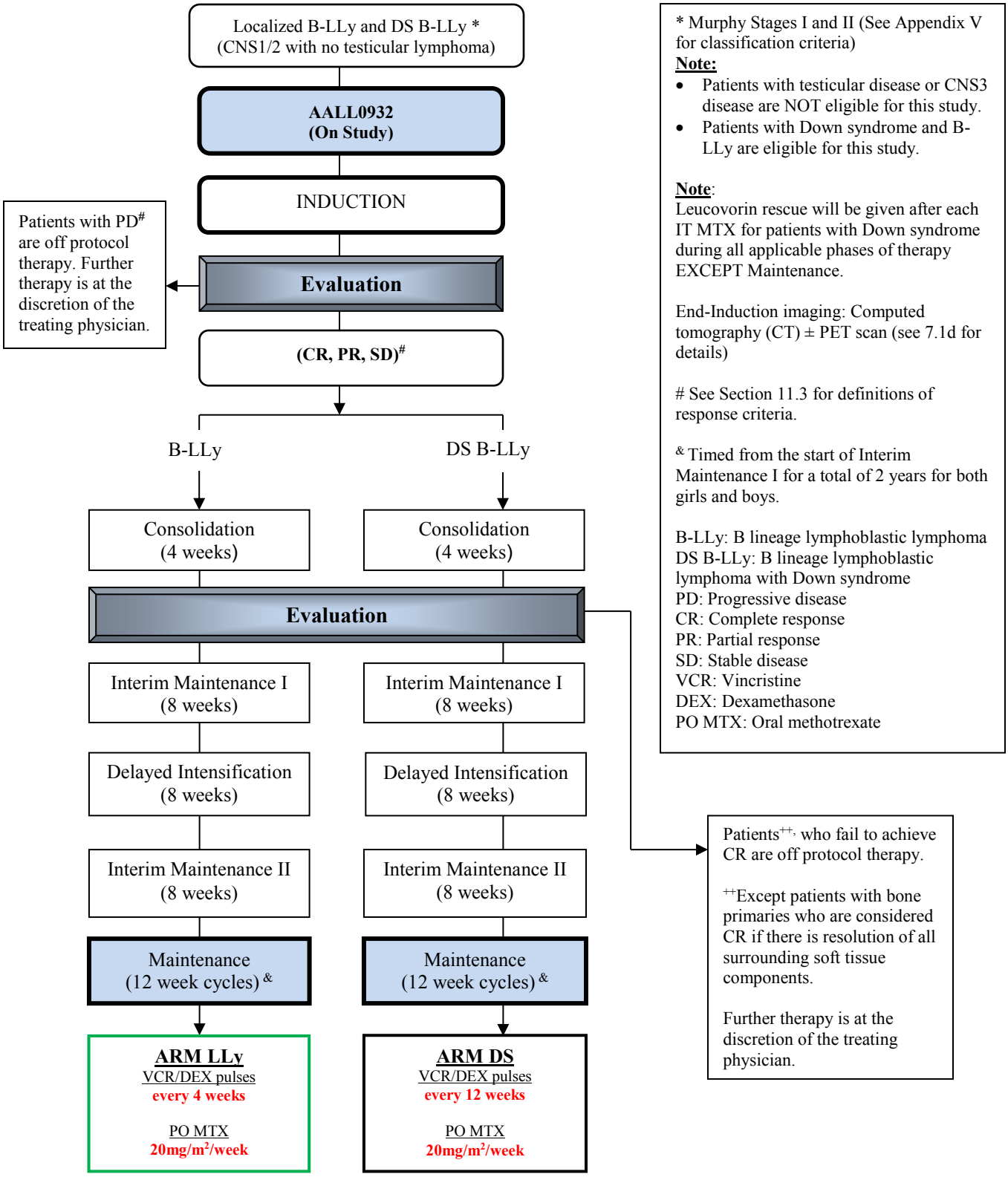
DS SR B-ALL: Day 29 BM MRD < 0.01%
AR B-ALL: (a) No favorable cytogenetics, CNS1 or 2, Day 8 PB MRD < 1% & Day 29 BM MRD < 0.01%; (b) favorable cytogenetics, Day 29 BM MRD < 0.01%; and either Day 8 PB MRD ≥ 0.01% or CNS2.
LR B-ALL: Favorable cytogenetics, CNS1, Day 8 PB & Day 29 BM MRD < 0.01%

Favorable cytogenetics: *ETV6/RUNX1* (*TEL/AML1*) fusion or double trisomy of chromosomes 4 and 10

% Timed from the start of Interim Maintenance I for a total of 2 years for both girls and boys.

DS SR B-ALL-Standard risk with Down syndrome
LR B-ALL –Low Risk
AR B-ALL –Average Risk
HR B-ALL – High Risk
VHR B-ALL – Very High Risk
VCR-vincristine
DEX-dexamethasone
PO MTX-oral methotrexate

EXPERIMENTAL DESIGN SCHEMA (B-LLy and DS B-LLy Patients)



* Murphy Stages I and II (See Appendix V for classification criteria)

Note:

- Patients with testicular disease or CNS3 disease are NOT eligible for this study.
- Patients with Down syndrome and B-LLy are eligible for this study.

Note:
Leucovorin rescue will be given after each IT MTX for patients with Down syndrome during all applicable phases of therapy EXCEPT Maintenance.

End-Induction imaging: Computed tomography (CT) ± PET scan (see 7.1d for details)

See Section 11.3 for definitions of response criteria.

& Timed from the start of Interim Maintenance I for a total of 2 years for both girls and boys.

B-LLy: B lineage lymphoblastic lymphoma
DS B-LLy: B lineage lymphoblastic lymphoma with Down syndrome
PD: Progressive disease
CR: Complete response
PR: Partial response
SD: Stable disease
VCR: Vincristine
DEX: Dexamethasone
PO MTX: Oral methotrexate

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

As current target accrual goals for AR patients have been met, there will be a sufficient number of patients enrolled and anticipated to be randomized in order to meet the following protocol objectives:

Primary Objectives: 1.1.1, 1.1.2, 1.1.3
Secondary Objectives: 1.2.1, 1.2.2

1.1 Primary Objectives

1.1.1
To determine if a Maintenance regimen containing weekly oral methotrexate at 40 mg/m²/week will result in an improved disease free survival (DFS) compared to that containing weekly oral methotrexate at 20 mg/m²/week in the AR subset of patients with Standard Risk B-ALL. **Complete effective January 13, 2017.**

1.1.2
To determine whether a reduced-pulses Maintenance regimen with vincristine/dexamethasone pulses delivered every 12 weeks can be used without adversely impacting DFS as compared to pulses given every 4 weeks in the AR subset of patients with Standard Risk B-ALL.

1.1.3
To confirm that patients in the LR subset of Standard Risk B-ALL, based on clinical and cytogenetic features and minimal residual disease (MRD) criteria, can attain a 5 year DFS of at least 95% with either a P9904 based regimen that includes 6 courses of intermediate dose (1 g/m^2 over 24 hours) methotrexate without alkylating agents or anthracyclines (Arm LR-M), or an outpatient based regimen identical to that of AR patients with reduced vincristine/dexamethasone pulses at 12 week intervals during Maintenance (Arm LR-C)

1.1.4
To provide standardized treatment and enhanced supportive care to children with SR DS B-ALL in order to improve outcomes and facilitate further study of this biologically and clinically unique patient subgroup.

1.1.5
To improve understanding of the biology of localized B-LLy and DS B-LLy by obtaining biologic data, including FISH for recurrent cytogenetic lesions on paraffin specimen, and banking tissue for future research.

1.1.6
To describe the 5-year EFS and overall survival (OS) of patients with Murphy Stage I and II B-LLy receiving modified AR B-ALL therapy.

1.2 Secondary Objectives

1.2.1
To assess the burden of AR B-ALL therapy as measured by surveys of the child's quality of life, missed days of school/daycare/work by children and parents, family functioning, parental perception of the child's health vulnerability, physical functioning, and emotional distress, 1) overall at different time points during and at the end of therapy, and by 2) comparing children randomized to every 4 week vs. every 12 week dexamethasone/vincristine pulses during Maintenance. **Closed to accrual as of April 19, 2013.**

1.2.2
To characterize the onset, severity, and natural history of vincristine associated neuropathy by physical therapists (or occupational therapists) in children undergoing therapy for AR B-ALL, 1) overall at different time points during and at the end of therapy, and by 2) comparing children randomized to every 4 week vs. every 12 week dexamethasone/vincristine pulses during Maintenance. **Closed to accrual as of March 15, 2013.**

1.3 Exploratory Objectives

1.3.1
To explore the correlation of minimal marrow disease (MMD) at diagnosis and outcome for patients with B-LLy. **Closed effective Amendment #5.**

2.0 BACKGROUND

2.1 Rationale for Selected Approach and Trial Design for B-ALL

After announcement/posting that accrual goals for the Average Risk (AR) B-ALL cohorts have been met, AR and Low Risk (LR) B-ALL patients will no longer receive post-Induction treatment on AALL0932. These patients will still be able to receive Induction treatment and risk stratification on AALL0932. Upon completion of Induction, AR and LR patients will come off protocol therapy. HR patients may be eligible for enrollment onto AALL1131 after Induction. There are no changes to enrollment for DS, B-LLy, or DS B-LLy patients.

AR and LR B-ALL patients enrolled before accrual goals for AR patients have been met will continue to receive Post-Induction treatment on AALL0932.

The merger of the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) into the Children's Oncology Group (COG) provided a unique opportunity to develop a new classification system that built upon the experience of both groups.[1] The outcome of over 8,000 patients was assessed with regard to clinical and biological variables tracked by both groups (NCI risk group, favorable or unfavorable cytogenetic features and early response to therapy). The goal was to define groups with different risks of relapse for which different post-Induction therapeutic questions could be asked. These analyses provided the rationale for the AALL03B1classification.

With data now mature from the P9900 series of acute lymphoblastic leukemia (ALL) studies, a revised risk stratification system has been developed and implemented in the second generations of COG trials for newly diagnosed ALL. The new classification study, AALL08B1, will continue to use a combination of NCI risk group, sentinel cytogenetic lesions, clinical variables (CNS and testicular status) and early treatment response. Day 8 and Day 15 bone marrow (BM) morphology will no longer be used to assess early response and will be replaced by minimal residual disease (MRD) in peripheral blood (PB) at Day 8 and BM at Day 29 of Induction therapy. Based on these findings, patients with B-lymphoblastic leukemia (2008 WHO classification), also termed B-precursor ALL will be stratified into 1 of 4 risk groups for post-Induction therapy: Low Risk (LR), Average Risk (AR), High Risk (HR), and Very High Risk (VHR) with projected 5 year EFS rates of greater than 95%, 90% to 95%, 75% to 90% and less than 75%, respectively.

This trial provides 3 drug Induction therapy to children with NCI SR B-lymphoblastic leukemia (B-ALL). At the end of Induction, children with SR B-ALL (without Down syndrome [DS]) will be further classified as LR or AR. Children with SR B-ALL and Down syndrome (DS SR B-ALL) will receive Induction and post-Induction therapy on a separate stratum of this protocol. The LR group consists of a selected group of

NCI SR patients with favorable cytogenetic features (*ETV6/RUNX1* formerly known as *TEL-AML1* fusion or simultaneous trisomies of chromosomes 4 and 10), CNS 1 status, PB MRD < 0.01% at Day 8 of Induction, and BM MRD < 0.01% at Day 29 of Induction and an estimated 5 year EFS of greater than 95%.[2] AALL0932 seeks to confirm that children with LR B-ALL can obtain outstanding outcomes using either a P9904-based regimen that includes 6 courses of intermediate dose (1 g/m^2 over 24 hours) methotrexate without alkylating agents or anthracyclines (Arm LR-M), or one identical to that of AR patients receiving regimen C Maintenance (see below) (Arm LR-C). Low-risk patients will be randomized between these 2 treatments arms. The goal will not be to prove superiority of 1 regimen, but rather to determine if excellent outcomes (at least 95% 5 year disease free survival) are obtained. The AR group consists of a selected group of NCI SR patients with favorable or neutral cytogenetic features who have Day 8 PB MRD < 1%, Day 29 BM MRD < 0.01% and an estimated 5 year EFS of approximately 92% - 94%. The estimated 2% - 3% of DS SR B-ALL patients will receive modified Induction and post-Induction therapy as part of this protocol, but will not be included in the randomized questions addressed in post-Induction therapy for SR children without DS because of their higher risk of treatment-related morbidity and mortality.

The most recent trial for NCI SR patients, AALL0331, asked one randomized question regarding the value of intensified vs. standard Consolidation following a 3 drug Induction for SR-Avg patients. The AALL0331 SR-Avg study previously asked a second question regarding the relative merit of augmented therapy during the Interim Maintenance (IM) and Delayed Intensification (DI) phases. AALL0331 was amended in Spring 2008, when maturation of data demonstrated a superior outcome associated with the use of escalating IV methotrexate/vincristine during IM on CCG-1991.[3] All rapid early responder (RER) patients on AALL0331 subsequently received this schedule of IV methotrexate and vincristine during a single IM phase, such that only the Consolidation question was studied in this population.

While data from AALL0331 regarding an optimal Consolidation regimen for these patients are maturing, AALL0932 explores the delivery of Maintenance therapy for children with the AR subset of SR B-ALL. This study compares 2 different doses of methotrexate during Maintenance administered with and without a reduced frequency of vincristine/dexamethasone (VCR/DEX) pulses, every 12 weeks compared to every 4 weeks, respectively, in a 2 x 2 design. Patients are randomized to 1 of 4 Maintenance regimens: **(A):** VCR/DEX pulses at 4 week intervals and oral methotrexate at 20 mg/m²/week (standard arm); **(B):** VCR/DEX pulses at 4 week intervals and oral methotrexate at 40 mg/m²/week; **(C):** VCR/DEX pulses at 12 week intervals and oral methotrexate at 20 mg/m²/week**;** and **(D):** VCR/DEX pulses at 12 week intervals and oral methotrexate at 40 mg/m²/week. Patients on all arms receive intrathecal methotrexate every 12 weeks during Maintenance and the duration of therapy will continue to be gender-based; namely 2 years from the start of IM I for girls and 3 years from the start of IM I for boys, consistent with recent COG ALL trials. The Data and Safety Monitoring Committee (DSMC) regularly monitors trial progress and released data that a futility boundary was crossed and that the study would not be able to demonstrate that 40 mg/m²/week of methotrexate is superior to 20 mg/m²/week of methotrexate. Effective January 13, 2017, a recommendation was made to reduce weekly methotrexate dose to 20mg/m^2/week, for all patients receiving 40 mg/m²/week of methotrexate during Maintenance. Subsequently, patients should have their doses of 6 mercaptopurine and methotrexate adjusted based on tolerability following normal dose escalation procedures, as outlined in the protocol Section 5.9.

2.1.1 Rationale for 2 Interim Maintenance Phases

CCG-1991 was a study for children with SR B-ALL, regardless of blast cytogenetic features. Patients with SR B-ALL with rapid early response to Induction therapy (Day 15 BM M1 or M2; M1 required if Day 8 BM was M3; Day 29 BM M1) and no unfavorable cytogenetic features (no t(9;22), balanced t(1;19), t(4;11), or hypodiploidy < 45 chromosomes were randomized in a 2 x 2 design to receive one or two DI phases and were also randomized to receive 2 different IM phases, one with oral MTX and one with IV escalating MTX without leucovorin rescue. There was no benefit to adding a second DI phase[3]; recent updates show 5 year EFS of 90.9 ± 1.3% for the single DI regimens, and 90.5 ± 1.3% for the double DI regimens (p =

0.71). The IV escalating methotrexate IM regimen was superior to oral methotrexate regimen, with 5 year EFS of 92.6 ± 1.2% vs. 88.7 ± 1.4% (log rank p = 0.009, RHR = 1.48).[3] Based on these results, children with AR B-ALL enrolled in AALL0932 will receive 2 IV methotrexate-based IM phases as given in CCG-1991 with a single DI phase (CCG 1991 regimen IS).

2.1.2 Rationale for a Randomized Comparison of Oral Methotrexate Doses During Maintenance

AALL0932 explores optimal oral methotrexate (MTX) dosing during Maintenance as this agent is a key component of Maintenance, or Continuation therapy. The poor bioavailability of oral MTX and inter-patient variability in plasma MTX levels following oral doses has been well documented.[4-7] Though incomplete absorption has been documented at all dose levels, saturation of absorption appears to occur at oral doses of approximately 40 mg/m^2,[6,7] suggesting that at doses of only 20 mg/m^2 absorption is not saturated for many patients. Higher oral doses may deliver more MTX and may enhance efficacy, either directly, or through inhibition of xanthine oxidase, which may decrease the first pass effect on the oral 6-mercaptopurine (6-MP) and increase its bioavailability[4,5,8,9].

Recent trials from both St. Jude Children's Research Hospital (SJCRH) and University of Texas Southwestern Medical Center/Dallas Fort Worth (DFW) have used weekly 40 mg/m^2 doses of MTX without excessive toxicity.[10,11] This higher weekly MTX dose of 40 mg/m^2 was administered orally in the DFW protocol and has been administered intravenously (IV) in SJCRH regimens, beginning in the mid-1980s. This dose of MTX has been well tolerated, in combination with daily doses of 6-mercaptopurine (6-MP) of 75 mg/m^2, during Continuation therapy. Specifically, on the Total XII protocol, among children who have the thiopurine S-methyltransferase (TPMT) wild-type phenotype, 84% of the oral 6-MP and parenteral methotrexate doses were delivered[12,13]. Although MTX has been administered IV or intramuscularly (IM) on SJCRH studies, differences in tolerability and outcomes were not observed on a United Kingdom (UK) ALL study which compared identical 20 mg/m^2 doses of MTX, administered IV/IM vs. orally [14]. In addition, nightly oral 6-MP at 75 mg/m^2 was well tolerated in combination with 40 mg/m^2 weekly oral methotrexate during Continuation therapy in a study of 243 children with ALL enrolled in the DFW protocol. This combination did not result in excessive toxicity and an overall EFS of 73% was observed among patients of all risk groups [11]. Notably, increased exposure to IV MTX in two 8-week IM phases also led to significant EFS improvements in CCG-1991 [3]

2.1.3 Rationale for the Recommendations of Dose Modifications for 6-MP and Methotrexate

For more than 10 years, dose modifications in the SJCRH ALL protocols have been based on a combination of measurements of thioguanine metabolites, TPMT status and clinical tolerance. This approach to 6-MP dose modification has enhanced the specificity of 6-MP dosing and optimized dosing of other agents during continuation therapy. Efforts have also been made to ensure the continuous delivery of MTX and 6-MP during Continuation as prior studies have demonstrated that interruptions in therapy due to profound neutropenia have correlated with inferior outcomes[12]. To this end, the threshold dose modification on SJCRH protocols has been lower than on recent COG studies. Specifically, full doses of MTX and 6-MP have been administered unless WBC falls below 1,500/µL, the ANC falls below 300/µL, or platelets fall below 50 000/µL or toxicity arises[12,15]. The dose modification section for AALL0932 has uniform modification guidelines for the arms of the study and is designed to facilitate continuous delivery of optimal doses of 6-MP and methotrexate, to ensure that the dose of methotrexate will differ between the treatment arms. For patients who do not tolerate their assigned MTX dose, TPMT testing and specific dose adjustments are recommended because there are compelling data demonstrating an inverse relationship between TPMT activity and thioguanine nucleotide (TGN) concentrations; with low TPMT activity and high TGN correlating with severe bone marrow suppression[16,17]. Guidelines for dose adjustments for patients who experience either significant myelosuppression or prolonged periods of high blood counts despite increased doses of 6-MP and MTX are included in protocol Section 5.9.

2.1.4 Rationale for a Randomized Comparison of Vincristine/Dexamethasone Pulse Frequency During Maintenance in Average Risk Subset of SR B-ALL

Given the excellent outcomes predicted for the SR patient population, another primary objective of this study will be to determine if these excellent outcomes can be maintained with every 12 week as opposed to every 4 week VCR/DEX pulses during Maintenance therapy. Reduced-pulses Maintenance will lessen the burden of therapy by decreasing cumulative exposure to dexamethasone and vincristine in Maintenance by two-thirds, with the aim of improving aspects of quality of life during therapy known to be affected by ALL treatment. These include vincristine-associated declines in fine motor and sensory-perceptual performance.[18] Dexamethasone is associated with myopathy-associated pain,[19] emotional lability, and disruptive behaviors.[20] The efficacy of vincristine/prednisone (VCR/PRED) pulses was first established in CCG-161 with lower risk patients randomized to receive or not receive monthly vincristine/prednisone pulses. There was a statistically significant improvement in EFS associated with the delivery of the pulses.[21] However, this therapy included a prednisone-based Induction, and no Delayed Intensification. Similarly, a meta-analysis of randomized ALL trials[22] showed a statistically significant advantage of vincristine/prednisone pulses on EFS, but there was no effect on overall survival (OS). The strongest effect on Maintenance therapy was seen in the 2 to 9 year old age group. However, this analysis was limited to trials that began before 1987, which are not reflective of contemporary therapy. None of the regimens used a dexamethasone-based Induction; none included a Delayed Intensification phase and overall EFS, was less than 70%. More recently, CCG-1891[23] administered a 3 drug prednisone Induction, and randomized intermediate risk B-ALL patients to receive one vs. two DI phases and every 3 week vs. every 4 week VCR/PRED Maintenance pulses in the context of a single DI phase. This study showed no advantage to more frequent Maintenance pulses.

The Berlin-Frankfurt-Münster (BFM) group has not typically used any vincristine/steroid pulses during Maintenance therapy and attains cure rates very similar to those obtained in COG trials. Recently, the I-BFM-SG ALL IR-95 trial randomized 2,935 intermediate risk patients to Maintenance regimens with and without six pulses that consisted of 7 days of DEX with VCR given on Days 1 and 8 of each pulse. The outcomes of the 2 groups were virtually identical with 7 year disease free survival rates of 77.5% with pulses and 78.4% without pulses, showing no benefit to pulses in the context of their treatment regimen[24]. Though this result is encouraging, it is not directly applicable to COG trials for SR patients since BFM therapy includes anthracycline therapy during Induction for all patients as well a more intensive Consolidation phase and 4 high dose MTX courses. Nevertheless, as summarized above, efficacy of vincristine/steroid pulses was only firmly established in regimens used during the 1970s and 1980s that did not use dexamethasone during Induction, did not administer a DI phase, and attained overall cure rates substantially below the 90% - 95% cure rate seen with modern SR B-ALL regimens.

In contrast, the European Organization for Research and Treatment of Cancer (EORTC) presented data in abstract form recently from their randomized Phase III 58951 study comparing 6 pulses of vincristine and corticosteroid every 10 weeks vs. no pulses during Continuation therapy in 411 children with average risk B-ALL (n = 384) and non-Hodgkin lymphoma (n = 27).[25] Superior outcomes were reported in those randomized to receive pulses with 6 year disease-free survival rates of 90.6% ± 2.1% vs. 82.2% ± 2.8%, (p = 0.027). Note, however, that given the overall duration of Maintenance therapy, the reduced pulses on AALL0932 still provides more vincristine and corticosteroid exposure than the “plus pulses” arm of that study. Some of the EORTC patients were included in the I-BFM-SG ALL IR-95 trial discussed above, which showed no benefit to VCR/DEX pulses in a much larger patient cohort.

It is also important to note that the COG P9904/5 trials administered VCR/DEX pulses every 12–16 weeks during Maintenance. While outcome for SR B-ALL patients enrolled in 9904/5 was modestly inferior to that obtained on CCG-1991 conducted at the same time, this difference is likely accounted for by the fact that more than half of patients enrolled in 9904/5 did not receive a DI phase, and therapy was not intensified for patients with a poor early response on 9904/5. Accordingly, there is precedent for using less frequent

VCR/DEX Maintenance pulses in recent COG trials and there are no compelling data to indicate that monthly pulses are needed in the context of more effective contemporary chemotherapy regimens. AALL0932 will definitely establish the role of monthly Maintenance VCR/DEX pulses in SR B-ALL.

A further potential benefit of reducing the number of VCR/DEX pulses during Maintenance is a reduction in the burden of therapy related to corticosteroids and vincristine. We specifically are interested in measuring if the less frequent Maintenance pulse schedule will improve altered self- and parent-reported quality of life in patients as documented in the ongoing AALL0331 study[26], parent perception of the child's health vulnerability[27], physical[28] and emotional functioning,[29] missed days of school/daycare by patients and work by parents[30,31], and vincristine-associated declines in fine motor and sensory-perceptual performance[18,32]. As discussed in detail later in this protocol document, we propose to directly assess these key outcomes in 2 integrated Health Related Quality of Life (HRQOL) ancillary studies (see protocol Sections 15.0 and 16.0). **UPDATE: Enrollment to both ancillary QOL studies is closed because accrual goals have been met.**

Patients with SR B-ALL without Down syndrome or LR features will be randomized immediately prior to the start of Maintenance therapy using a 2x2 design to 20 mg/m^2/week vs. 40 mg/m^2/week of methotrexate and every 4 week vs. every 12 week VCR/DEX pulses during Maintenance therapy. The baseline EFS expected for this SR group is uncertain, as this exact patient group has not been treated with this therapy in past studies. Patients that meet this SR definition had a projected 5 year EFS rate of 91% - 93% on P9900. The entire group of NCI SR B-ALL patients with a RER based on Day 15 BM status and no unfavorable cytogenetic features randomized to the IV MTX IM regimens had a 92.6% 5 year EFS on CCG-1991. This included many excellent risk patients with favorable genetic features that will not be included in this trial, but also included patients that were MRD positive at end-Induction. Thus we estimate that the baseline 5 year EFS for AR patients in AALL0932 will be 92% - 94% and have used 93% in the statistical design.

2.1.5 Inclusion of CNS 2 Patients in Average Risk Subset of SR B-ALL

Average Risk therapy is appropriate for AR patients with CNS2 status as CCG 1991, upon which this study is based, included 67 rapid responding CNS2 patients that participated in the 2x2 randomization. Their 5 year EFS and OS were 77% (SE = 8.3%) and 92.5% (SE = 5.2%) respectively, as compared to 90.7% ± 1.0%, and 96.0% ± 1.0% for the entire population of RER patients. Relapses in the CNS were double those in the BM in this subset of patients: 9 vs 4. However, the IV methotrexate based IM regimens used in CCG 1991 provided significant overall benefit that was entirely due to protection from extramedullary relapse. Overall on CCG 1991, the patients randomized to the IV methotrexate arms experienced 11 CNS, 5 BM + CNS, and 0 testicular relapses. In comparison, patients randomized to the oral MTX based IM regimens experienced 26 CNS, 10 BM + CNS, and 7 testicular relapses. While numbers are small for the CNS2 patients, the incidence of isolated CNS relapses in patients with CNS2 status randomized to the IV MTX regimens was less than a third that for those randomized to the PO MTX containing regimens (2/35 vs. 7/32).[3] The combination of dexamethasone in Induction and IV methotrexate during two IM phases appears to provide excellent CNS protection for this group. CNS2 patients are explicitly excluded from the low risk group.

2.1.6 Low Risk Subset of SR B-ALL

Low risk patients will be randomized to 1 of 2 post-Induction therapies on AALL0932. The first regimen (Arm LR-M) is based on the excellent outcomes with P9904 therapy (Figure 1). Patients who were NCI SR with favorable genetics who lacked CNS or testicular disease, and who had MRD < 0.01% at Day 8 (PB) and Day 29 (BM) achieved a 5 year EFS of 97 ± 2% (SE 0.01%) and OS of 98.8 ± 0.8% on P9904.[2] P9904 randomized NCI SR patients with the *ETV6/RUNX1* fusion to 1 of 2 methotrexate infusion schedules (1 g/m^2 over 24 hours vs. 2 g/m^2 over 4 hours) and ± DI. Patients with trisomies 4 & 10 were included in the methotrexate randomization only. Accordingly, approximately 25% of these patients were randomized to receive a DI phase, while the other 75% were randomized or assigned to no DI. There is no suggestion of

benefit to DI among these patients with favorable cytogenetics and no differences in outcome have been observed with the different methotrexate schedules. Among 261 patients there have been only 8 events, including 6 relapses and 2 second malignant neoplasms. It is unlikely that this outcome will deteriorate significantly; to date there has been only 1 event among the 179 patients that are more than 5 years from study entry. We anticipate this will translate into long-term EFS of greater than 95%. In addition, patients from this group that relapse still have a significant chance of cure. A total of 6 patients have relapsed in this group treated on P9904 (2 DI arm, 4 No DI arm). Three were early relapses (< 36 months from diagnosis), and 3 were late relapses (≥ 36 months from diagnosis). Three remain alive as of 06/01/2009 (1 early and 2 late relapses).

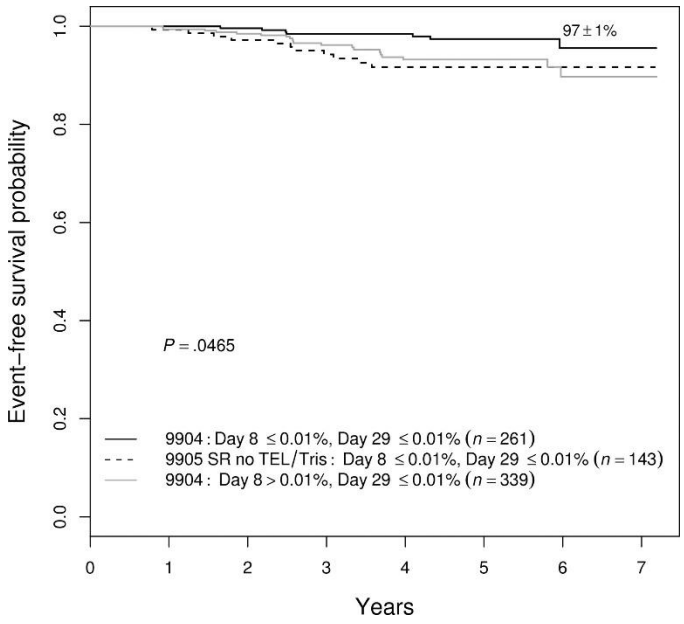


Figure 1. EFS among variably defined groups of good-prognosis patients. NCI SR patients with favorable genetic features who were MRD-negative at both Day 8 and Day 29 were the best group, with a 97% ± 1% 5 year EFS. They had statistically better outcomes than either patients without the genetic features who had the same MRD characteristics (92% ± 3%; *P* = .020) or end-Induction MRD negative, favorable genetic patients who were Day 8 MRD positive (93% ± 2%; *P* = .024)[2]

Although the evidence on late effects of anthracyclines[33,34] and alkylating agents at doses used in CCG-1991 is inconclusive, it seems prudent to investigate the P9904 regimen that has no exposure to these agents given their toxicity and the outstanding EFS attained for LR patients treated without these agents on P9904. Note that in a study of 40 pediatric patients with B-ALL who had received only 90 mg/m^2 of anthracycline, more than 20% had an abnormal left ventricular fractional shortening or afterload.[35]

The second regimen (Arm LR-C) is based on the outstanding results from CCG-1991 that form the backbone for the AR subset. As described in Section 2.2 above, the superior outcome for patients receiving Interim Maintenance with intravenous methotrexate compared to oral methotrexate has been reported.[3] Narrowing our focus to outcome for patients with genetic abnormalities eligible for the LR arm, but without regard to whether or not they received the more effective intravenous methotrexate regimen or MRD status, 6 year EFS for randomized patients with trisomy 4 & 10 and *ETV6/RUNX1* was 94.5 ± 2.2% and 92.9 ± 2.6% and 6 year overall survival was 98.6 ± 1.1% and 98.1 ± 1.1%, respectively.[36] Thus, even without using a filter to remove patients with Day 8 peripheral blood MRD or Day 29 bone marrow MRD > 0.01%, the 6 year EFS for patients receiving 2 intravenous methotrexate-based IM phases as given in CCG-1991 will likely approach or exceed 95% for each of these groups. While intermediate dose methotrexate had been

administered as a 20 minute bolus followed by a 23.67 hour infusion on P9904, PK modeling demonstrates no difference in MTX plasma concentration when given as a 30 minute bolus followed by a 23.5 hour infusion (Frank Balis, personal communication). Administration with either of these schemas will be allowed based on institutional preference. One modification to the CCG-1991 therapy that will be implemented in this regimen is a reduction in the frequency of VCR/DEX pulses to q12 week from q4 weeks (as in Arm C of the AR subset). Given this outstanding expected outcome, the LR patients randomized to this treatment strategy will be non-randomly assigned to receive VCR/DEX pulses every 12 weeks. This important modification is likely to benefit patients by reducing the burden of therapy.

Thus, there is strong evidence indicating that LR patients can attain a 5 year DFS of > 95% and OS of 98% - 99% with either the COG P9904 or CCG-1991 based regimens. This study seeks to validate a very important finding, namely that the specific low risk criteria we now define prospectively can identify a subset of patients almost certain to be cured. We believe that this is an important goal that has major implications for treatment of childhood ALL, and will indeed provide new information. Each regimen has relative advantages and disadvantages compared to the other regimen. The COG P9904 therapy includes no anthracyclines or alkylating agents, but requires 6 hospitalizations to deliver 24 hour methotrexate infusions with accompanying blood draws to monitor methotrexate clearance and additional clinic visits during Maintenance. In contrast, the CCG-1991 based regimen includes no inpatient therapy following Induction, but during Delayed Intensification may lead to hospitalizations for fever and neutropenia, transfusions of blood products and includes 75 mg/m^2 of anthracyclines and 1 g/m^2 of alkylating agents. Given these factors, LR patients will be randomized at the conclusion of Induction therapy to 1 of these 2 regimens. The goal will not be to prove superiority of 1 regimen, but rather to determine if excellent outcomes (at least 95% 5 year DFS) are obtained. If both regimens meet this benchmark, then physicians can select the optimal treatment approach based on the needs of the patients and families.

2.1.7 Children with SR B-ALL and Down syndrome

Approximately 2% - 3% of children with ALL have Down syndrome, and these DS B-ALL patients have an increased risk of treatment related mortality.[37] Recently, COG suspended accrual of DS B-ALL children to trials for SR (AALL0331) and HR (AALL0232) B-ALL because of excess mortality.[38] The trials were subsequently reopened after treatment modifications for DS B-ALL patients were introduced. Following this safety amendment, there have not been excess deaths among DS SR B-ALL patients enrolled in AALL0331; but continued excess mortality among HR B-ALL patients led to permanent closure of AALL0232 to patients with DS in January 2008.[38] The goal of the DS stratum on this protocol is to improve outcomes in children with DS and B-ALL by providing effective therapy, while reducing early deaths from toxicity. DS children have therefore been assigned to a DS-specific single-arm, risk based therapeutic regimen for Induction and post-Induction therapy, designed in consideration of their increased incidence of treatment-related morbidity and mortality. Parents of patients enrolled on this therapeutic trial will have the opportunity to consent to optional banking of leukemia and germline specimens on AALL08B1, which will facilitate ongoing research to better understand this small but biologically distinct and clinically challenging group of patients. Enhanced supportive care guidelines and toxicity monitoring for DS patients are included (see Section 8.3) with the goals of prospectively studying treatment related toxicities, and minimizing their occurrence. Collection of targeted data on IgG levels, infectious toxicities and febrile neutropenia on AALL0932 will identify the relevant types of infectious organisms, sites of infection, timing during ALL therapy, and the role of risk factors such as neutropenia and IgG in a large, uniformly treated DS B-ALL cohort. The resulting data will provide much-needed evidence for the development of improved supportive care recommendations for this subset of B-ALL patients with increased susceptibility to life threatening infections.

For DS SR B-ALL patients, the therapeutic changes instituted by the AALL0331 safety amendment consisted of leucovorin rescue after intrathecal methotrexate in an attempt to mitigate the known enhanced sensitivity to methotrexate toxicity associated with DS[39,40], along with elimination of a second DI phase,

use of interrupted dose dexamethasone during DI phases, and enhanced supportive care recommendations As there has been no excessive treatment related mortality among 93 NCI SR DS patients (as of 9/29/2009) enrolled since modifications to AALL0331 were instituted, this study will administer Induction therapy identical to that given in AALL0331 for NCI SR DS patients except pegaspargase will be administered IV. All NCI SR DS patients will be eligible for the DS Induction stratum on this protocol with the exception of patients with CNS involvement, testicular disease, or steroid pretreatment.

Following Induction therapy, DS patients with Induction failures or the Philadelphia chromosome will not be eligible to continue on a COG ALL trial. Standard risk DS patients that have Day 29 BM MRD ≥ 0.01%, *KMT2A* (*MLL)* rearrangement, or hypodiploidy are not eligible to receive post-Induction therapy on this trial, but will be eligible for post-Induction therapy on the HR protocol. Post-Induction therapy for the remainder of NCI SR DS patients is similar to the 1991 IS arm with AALL0331 modifications (including leucovorin rescue following intrathecal MTX in all phases prior to Maintenance therapy) for DS patients with the exception of reduced frequency VCR/DEX pulses during Maintenance. Two IM phases with IV methotrexate were well tolerated among the DS patients on CCG-1991. With the exception of Grade 3 or higher stomatitis, which occurred in 28.1% of DS patients who received IV methotrexate during IM#1 and 26.7% of DS patients during IM #2, all other Grade 3 or higher toxicities observed with escalating IV methotrexate during IM were infrequent in children with DS B-ALL. The 5 year EFS for the 77 eligible RER DS SR B-ALL patients enrolled on CCG-1991 was 90.1 ± 4.9% overall; with the randomized RER DS B-ALL patients attaining 5 year EFS of 83.3 ± 7.6% with oral methotrexate (n = 45) and 100% with IV methotrexate (n = 32, p = 0.022). Therefore, the IV MTX based IM regimen is safe and highly effective for children with SR DS B-ALL and the CCG-1991 Regimen IS will be used for these patients on AALL0932 with AALL0331 modifications (including leucovorin rescue following intrathecal MTX in all phases prior to Maintenance therapy). Two other differences will be that DS B-ALL patients will be non-randomly assigned to every 12 week VCR/DEX pulses during Maintenance, and treatment duration will be 2 years from the start of IM#1 for both boys and girls with DS. These changes were made because of the increased risk of fatal infectious complications in children with DS B-ALL, which may be heightened by the immunosuppressive effects of steroids. Deaths during Maintenance therapy occurred in two HR DS B-ALL patients on AALL0232 prior to study closure (E. Larsen, M.D personal communication), and 4 DS patients enrolled on the UK ALL 2003 study (A. Vora, M.D, personal communication).

2.1.8 Exclusion of Patients with Intrachromosomal Amplification of Chromosome 21 (iAMP21) from Post-Induction Therapy on AALL0932

The outcome of patients with intrachromosomal amplification of chromosome 21 (iAMP21) has been monitored during the conduct of COG AALL0232 and AALL0331. This monitoring was based on reports from other groups of inferior outcomes associated with iAMP21.[41-43] COG ALL trials detect iAMP21 due to FISH screening for the *ETV6-RUNX1* fusion. While earlier analyses suggested that iAMP21 patients had outcomes similar to those of non-iAMP21 patients on COG AALL0232 and AALL0331, new analyses with larger patient numbers and longer follow-up have shown that the outcome of children with iAMP21 is significantly worse than the outcome of those without iAMP21 (Meenakshi Devidas, PhD, unpublished data, June 2011). Among NCI SR patients treated on AALL0331 the outcomes for iAMP21 patients (n = 75) were inferior to non-iAMP21 patients (n = 4,985) overall (4 year EFS 70.4% SE 9.3% vs. 91.8% SE 0.7%; p < 0.0001) and among those with Day 29 MRD < 0.01% (4 year EFS 81.1% SE 11.1% vs. 94.1% SE 0.7%) and those with Day 29 MRD ≥ 0.01% (55.6% SE 15.1% vs. 84.2% SE 2.2%). Therefore with Amendment #1, patients enrolled in AALL0932 that are identified to have iAMP21 will be classified as Very High Risk and will not be eligible to continue on AALL0932 after Induction therapy, but will be eligible to enroll in AALL1131 for post-Induction therapy.

2.2 **Rationale for Selected Approach and Trial Design for Patients with B-LLy**

Children and adolescents with lymphoblastic lymphoma (LLy) are currently treated with therapy derived from ALL protocols with disease free survival approaching 80% - 90%. There is a precedent to expand

ALL trials to include LLy patients, including enrollment of T-NHL patients on AALL0434, and enrollment of relapsed T-NHL patients on AALL07P1. Accrual of NHL patients to both of these trials has been more robust than anticipated, suggesting overcoming regulatory burdens by enrolling NHL patients to ALL trials can increase enrollment and capture of important biological and outcome data.

COG A5971 enrolled patients with B- and T-LLy with modified BFM type ALL therapy. A5971 stratified patients by stage (localized [Murphy Stage I and II] versus disseminated [Murphy Stage III and IV]) and not by immunophenotype. Out of 380 total accruals, only 11% of patients (n = 42) had precursor B phenotype. However, 75% of all patients with localized disease had precursor B phenotype. Those patients were enrolled an Arm A0 and received a 4 drug Induction followed by intensified Consolidation with cyclophosphamide, cytarabine and mercaptopurine, Interim Maintenance with mercaptopurine and PO methotrexate, and standard Delayed Intensification and Maintenance for a total therapy length of 2 years from the start of Induction. The outcome of patients with localized B-LLy was a 5 year EFS of 90% (95% CI: 74% - 96%) and a 5 year OS of 94% (95% CI: 79% - 99%).

The NHL-BFM study group reported a 5 year-EFS of 86% (SE = 4%) in 73 patient with B-LLy treated on NHL-BFM 90 and 95. Among the B-LLy, 27 patients had Murphy Stage I and II, 3 of whom relapsed. Therapy consisted of intensive ALL type therapy that included intensified Consolidation (part of Induction I in NHL-BFM) and high dose methotrexate in Interim Maintenance (protocol M). Patients with localized disease (Murphy Stage I and II) did not receive a Delayed Intensification phase (Re-induction I) which reduced the total anthracycline exposure to 120 mg/m^2.[44]

The French reported on 53 children with B-LLy treated on 2 consecutive protocols (LMT 96, EORTC 58881 and 58951) using BFM derived ALL therapy. LMT96 included cyclophosphamide and high dose methotrexate (3 g/m^2) in Induction and high dose methotrexate (3 g/m^2) in Consolidation but the 2 consecutive protocols had a standard 4 drug Induction followed by intensified Consolidation as used in high risk ALL. All protocols used HD MTX in Interim Maintenance (3 g/m^2 x2 in LMT96, 5 g/m^2 x 4 in EORTC 5881 and 58951). Nineteen of 53 patients had localized disease (Murphy Stage I and II). Patients with localized disease received only 2 doses of daunorubicin in Induction and Delayed Intensification, respectively, reducing total anthracycline exposure to 120 mg/m^2 and did not receive any cyclophosphamide either in Consolidation or Delayed Intensification[44] in EORTC 58881 and 58951. There were no relapses reported in the localized group.[45]

These data from 3 cooperative groups confirm the excellent outcome patients with B-LLy have with ALL derived therapy. Furthermore, A5971 demonstrated that the excellent outcome was preserved without the use of HD MTX in Interim Maintenance. Starting with Amendment #2A, patients with localized B-LLy (Murphy Stage I and II) will be non-randomly assigned to the standard arm for AR B-ALL with Maintenance “Arm LLy”. Patients with localized B-LLy (Murphy Stage I and II) and DS will be non-randomly assigned to DS SR B-ALL with Maintenance “Arm DS”.

2.2.1 The Rationale for a 3 Drug Induction and Standard Consolidation in B-LLy patients

The use of a 3 drug Induction instead of a 4 drug Induction reduces the total anthracycline dose to 75 mg/m^2 compared to 175 mg/m^2 and the use of standard Consolidation instead of intensified Consolidation reduces cyclophosphamide exposure from 3 g/m^2 to1 g/m^2. The BFM and EORTC groups have shown that dose reductions in anthracyclines and cyclophosphamide are feasible. Both the BFM-NHL and EORTC protocols used an anthracycline dose of 120 mg/m^2 and EORTC did not give any cyclophosphamide to B-LLy patients with Murphy Stage I and II without jeopardizing outcome. It is hypothesized that these dose reductions will not affect outcome and may reduce late effects.

2.2.2 The Rationale for Dexamethasone in Induction

B-LLy patients regardless of age on AALL0932 will receive dexamethasone as the sole corticosteroid during therapy (versus prednisone in A5971). Dexamethasone has been shown in several studies to be superior to prednisone in reducing CNS relapses.[46-48] A recent meta-analysis of dexamethasone versus prednisone included 8 cooperative group studies confirmed the reduction in CNS relapses and showed no increased risk of osteonecrosis with dexamethasone versus prednisone. The only study showing an increased risk of osteonecrosis in children > 10 years of age was AALL0232; but the dose of dexamethasone was higher at 10 mg/m^2. EORTC58951 which enrolled patients up to 18 years of age and randomized between prednisone (60 mg/m^2 x 28 day) and dexamethasone (6 mg/m^2 x 28 days) did not show an increased risk of osteonecrosis in the dexamethasone arm.

2.2.3 Rationale for 2 Interim Maintenance Phases with Capizzi Methotrexate in B-LLy

In A5971, patients with localized B-LLy enrolled on Arm A received a single Interim Maintenance phase with oral methotrexate and mercaptopurine. Both EORTC and BFM use HD MTX in Interim Maintenance. In patients with SR B-ALL enrolled on CCG-1991, the IV escalating methotrexate IM regimen was superior to oral methotrexate regimen, with 5 year EFS of 92.6 ± 1.2% vs. 88.7 ± 1.4% (log rank p = 0.009, RHR = 1.48). Based on these results, children with B-LLy enrolled in AALL0932 will receive 2 IV methotrexate-based IM phases as given in CCG-1991 with a single DI phase (CCG 1991 regimen IS).

2.2.4 Rationale for Tissue Collection and Banking in B-LLy patients

A5971 had very limited specimen collection, particularly in the low stage patients. Only 60% of patients had central review of their pathology. There are currently no well defined biological prognostic markers for B-LLy.

2.2.5 Rationale for Minimal Marrow Disease Testing at Diagnosis

Minimal marrow disease (MMD) has been shown to be present in 80% of Stage III T-LLy at diagnosis.[49] On COG AALL0434, MMD is measured at diagnosis in all T-LLy patients enrolled. The importance of MMD in B-LLy is currently not known. AALL0932 asks for a single bone marrow at diagnosis to be sent for MMD testing and will explore whether it correlates with outcome. Due to changes in funding mechanisms and the move to fee per service decentralized MMD testing, effective Amendment #5 diagnostic MMD for B-LLy patients is closed.

2.2.6 Rationale for Tissue Banking on Subsequent Biologic Studies

The prognostic significance of recurrent cytogenetic abnormalities in B-ALL has been well described and patients with B-ALL are currently risk stratified based on the cytogenetic profile of their blasts. There is a paucity of data on cytogenetic abnormalities in B-LLy because in prior studies both obtaining and successfully performing cytogenetic analyses on fresh tissue has been difficult. Biology studies will include a limited cytogenetic analysis by fluorescence in-situ hybridization (FISH) combined with single nucleotide polymorphism (SNP) analysis. The advantage of these methods is that they can be performed on formalin fixed paraffin embedded (FFPE) tissue. If they prove feasible they will be the tool for a better classification of B-LLy.

2.3 **Development Plans**

AALL0932 seeks to refine Maintenance therapy for patients with SR B-ALL by defining an optimal MTX dose and reducing the burden of therapy by reducing the frequency of VCR/DEX pulses. HRQOL measures, parent's perception of child's health vulnerability, fewer missed days of school/daycare by patients and work by parents and peripheral neurological functioning will be compared in children receiving different VCR/DEX pulses frequencies to systematically assess the impact of treatment. These proposed changes will occur exclusively during the Maintenance phase of therapy while data from AALL0331 are maturing. AALL0331 seeks to define the optimal Consolidation therapy for a very similar patient population. We anticipate that the best arm of AALL0932, paired with the optimal Consolidation schedule determined in

AALL0331, will become the standard regimen for patients with SR B-ALL in future studies. The results of AALL0932 will have important implications for other ALL risk groups. For example, if excellent outcomes are preserved with a reduction in VCR/DEX exposure in these SR patients, a similar reduction could be considered for NCI high risk patients, where osteonecrosis is a much more significant concern. Further, if a higher dose of methotrexate improves outcomes and is not associated with excess toxicity, this dosage could be adopted in Maintenance regimens for other risk groups. Finally, the success of this study will depend on strict adherence to dosing modification guidelines for oral methotrexate and 6-MP and the guidelines used in this study could similarly be incorporated into trials for other risk groups with the potential for individualization of dosing using TPMT status, among other parameters, in the future. Another important goal of this trial is to confirm that children with LR B-ALL can attain > 95% 5 year DFS with either a P9904-based regimen that includes no alkylating agents or anthracyclines (Arm LR-M) or a CCG 1991-based regimen with vincristine/dexamethasone pulses at 12 week intervals during Maintenance (Arm LR-C). If both regimens meet this benchmark, then physicians and families can select the treatment that they prefer for LR B-ALL patients in the future. Finally, another important goal of this study to provide safe and standardized therapy to DS patients with SR B-ALL, and to facilitate further study of this biologically and clinically unique subgroup.

By including patients with localized B-LLy, this protocol will offer a unified approach to the treatment of all patients with standard risk B lymphoblastic lymphoma/leukemia and may lead to a reduction of late effects by reducing the dose of cyclophosphamide and anthracycline exposure in B-LLy patients. The exploration of MMD and cytogenetic abnormality by FISH may lead to better risk stratification of B-LLy patients in the future.

2.4 Patient Enrollment After AR B-ALL Accrual Goals Have Been Met

After announcement/posting that accrual goals for the Average Risk (AR) B-ALL cohorts have been met, AR and Low Risk (LR) B-ALL patients will no longer receive post-Induction treatment on AALL0932. These patients will still be able to receive Induction treatment and risk stratification on AALL0932. Upon completion of Induction, AR and LR patients will come off protocol therapy. HR and VHR patients may be eligible for enrollment onto AALL1131 after Induction. There are no changes to enrollment for DS, B-LLy, or DS B-LLy patients.

AR and LR B-ALL patients enrolled before accrual goals for AR patients have been met will continue to receive Post-Induction treatment on AALL0932.

2.5 Rationale for additional IT therapy for Non-Down Syndrome (Non-DS) B-Acute Lymphoblastic Leukemia (B-ALL) Patients with Central Nervous System 2 (CNS2) Disease (Amendment # 4)

Results of COG AALL0232 and AALL0331 for patients with non-DS B-ALL demonstrate significantly inferior outcomes for patients with CNS2 and CNS3 disease compared to those with CNS1 status. The 5 year event free survival (EFS) for patients with CNS2 versus CNS3 and CNS1 treated on AALL0232/0331 were 76 $\pm$2%, 76 $\pm$5.2% and 85 $\pm$0.6%, respectively ($p < 0.001$). [*Personal communication, M. Devidas*] These differences in EFS are largely the result of CNS relapse rather than bone marrow relapse. The incidence of isolated and combined CNS relapse for patients with CNS1 status on AALL0232/AALL0331 was 2.9 $\pm$0.2% versus 7.8 $\pm$0.98% for CNS2 and 5.9 $\pm$2.2% for CNS3 ($p < 0.001$). Additionally, there was no significant difference in the rate of bone marrow relapse based on CNS status (CNS1 versus CNS2/3; $p = 0.1815$). No difference in EFS was seen between patients with CNS2 due to a traumatic lumbar puncture (TLP) versus CNS2 without a TLP ($p = 0.333$). In multivariate analysis comparing CNS1 to CNS2/CNS3, CNS status remained significant (HR 1.501, 95% CI 1.21 – 1.86; $p = 0.0002$). When analyzing the NCI standard risk (SR) and high risk (HR) patients separately, CNS2/3 disease continued to predict worse outcome for both risk groups. SR patients with CNS1

status on AALL0331 had a 5 year EFS of 90 ±0.6% compared to 85 ±2% for CNS2 and 82 ±7% for CNS3 ($p = 0.0003$) and HR patients on AALL0232 with CNS1 status had 5-year EFS of 77 ±1% compared to 67 ±3% for CNS2 and 71 ±7% for CNS3 ($p < 0.0001$).

Systemic and intrathecal therapy for HR non-DS B-ALL patients with CNS1 or CNS2 on COG study AALL0232 was identical. Only patients with CNS3 disease received more intensive CNS-directed therapy during Induction with weekly intrathecal (IT) methotrexate on Days 8, 15, 22 and 29 compared to patients with CNS1/2 who received IT methotrexate only on Days 8 and 29. Patients with CNS3 disease did not receive IT therapy on Days 15 and 22 of Consolidation but did receive cranial radiation (1,800 cGy) during Delayed Intensification. The legacy POG protocols gave additional IT therapy to patients with CNS2 disease, legacy CCG protocols did not, with both demonstrating a modest increase in risk associated with CNS2 disease. The Dana Farber Cancer Institute ALL study DFCI 00-01 gives twice weekly IT cytarabine until the cerebral spinal fluid (CSF) clears for three consecutive lumbar punctures during Induction and the Berlin-Frankfurt-Munster (BFM) group includes two additional doses of IT methotrexate during Induction for CNS2/3 patients. It should be noted, however, that the BFM protocols use less overall IT therapy than the COG protocols. St. Jude Children's Research Hospital gives IT cytarabine Day 1 (as does COG for all patients) followed by twice weekly Intrathecal Triple Therapy (ITT) (cytarabine, hydrocortisone, methotrexate) in patients with CNS2/3 disease until the CSF is clear of blasts.

Given the significantly inferior EFS reported for non-DS B-ALL patients with CNS2 disease treated on AALL0331 and AALL0232 and the available safety data on the use of more frequent IT therapy during Induction, we are modifying Induction on AALL0932 for patients with CNS2 disease such that they will receive twice weekly intrathecal therapy during Induction until 3 consecutive CSF samples after diagnosis are clear of blasts. Patients should receive additional IT Cytarabine on Days 4, 5 or 6 during Induction (depending on treatment schedule), IT Methotrexate on Day 8, and then IT Cytarabine on Days 11 or 12. If the CSF at all three of these time points is negative for blasts, patients will receive their next IT therapy with methotrexate on Day 29. If the CSF remains positive after the initial LP, patients will continue IT Cytarabine twice weekly during Induction until the CSF is clear for three consecutive LPs. All patients will receive IT therapy with methotrexate on Day 29 at the end of Induction regardless of CSF evaluations.

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

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 with a known or suspected neoplasm needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)* or APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

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.

Please see Appendix VI for detailed CTEP Registration Procedures for Investigators and Associates.

3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the Cancer Trials Support Unit (CTSU) Regulatory Office before they can be approved to enroll patients. 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 submitted via the online portal via www.ctsu.org in the member's section, under the Regulatory Submission Portal where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1 (888) 823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

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 or the Callback process, email a request for assistance to the COG Help Desk and copy the AALL0932 Research Coordinator. See Section 3.1.7 below for full details regarding randomization and treatment assignment for patients with LR B-ALL, AR B-ALL, DS SR B-ALL, B-LLy and DS B-LLy.

3.1.4 Timing

PATIENTS WITH B-ALL MUST BE ENROLLED ON COG AALL08B1 OR PROJECT:EVERYCHILD (APEC14B1, IF OPEN FOR CLASSIFICATION OF NEWLY DIAGNOSED ALL PATIENTS) BEFORE PROTOCOL THERAPY BEGINS (For the purposes of this study, 'protocol therapy' does not include the first dose of intrathecal chemotherapy or selected cases of steroid pretreatment). **PATIENTS THAT BEGIN PROTOCOL THERAPY ON THIS STUDY PRIOR TO ENROLLMENT ON AALL08B1 (OR APEC14B1) ARE INELIGIBLE FOR AALL0932.**

PATIENTS WITH B-LLy ARE NOT ELIGIBLE FOR ENROLLMENT ON AALL08B1 AND CAN ENROLL DIRECTLY ON AALL0932. EVERY EFFORT SHOULD BE MADE TO ACQUIRE AS MUCH TISSUE AS POSSIBLE. SPECIFIC INSTRUCTIONS REGARDING TISSUE SUBMISSION ARE OUTLINED IN SECTION 14.0.

All Patients:

Informed consent: Except for administration of intrathecal cytarabine or allowable steroid pretreatment (defined below), *informed consent/parental permission* MUST be signed before protocol therapy begins.

Study enrollment: Study enrollment (completion of forms in RDE) must take place no later than five (5) calendar days after beginning protocol therapy. If study enrollment takes place *before* starting protocol therapy, the date protocol therapy is projected to start must be no later than ***five (5)*** calendar days after enrollment.

Eligibility studies:

B-ALL:

Patients must meet all eligibility criteria prior to the start of protocol therapy or enrollment, whichever occurs first. Unless otherwise indicated in the eligibility section below, all clinical and laboratory studies to determine eligibility must be performed within 7 days prior to the start of protocol therapy or enrollment whichever occurs first.

B-LLY:

Patients must meet all eligibility criteria prior to the start of protocol therapy or enrollment, whichever occurs first. Unless otherwise indicated in the eligibility section below, all staging studies to determine eligibility must be performed within 7 days prior to the start of protocol therapy or enrollment whichever occurs first. The diagnostic biopsy however, does not have to be done within this 7 day time period.

Initiation of systemic protocol therapy: Systemic Induction chemotherapy, with the exception of steroid pretreatment as outlined below, must begin within 72 hours of the first dose of intrathecal chemotherapy.

3.1.5 Staged Consent

Informed consents will be obtained at critical stages of treatment for the different groups of patients on this study. The required consents are different for patients enrolled prior to accrual goals being met than for those enrolled after accrual goals have been met (see summary tables below).

Informed consent that describes the first 4 weeks of Induction therapy will be obtained for all patients before starting treatment. All patients will receive a common Induction regimen with the exception of children with DS SR B-ALL or DS B-LLy, who will also receive 2 doses of oral leucovorin following each dose of intrathecal methotrexate during Induction. Patients with B-LLy and DS B-LLy will be approached with a single consent prior to starting Induction therapy, which describes all therapy to be received on study.

For patients enrolled before accrual goals for AR patients has been met and all DS B-ALL patients:
At the end of Induction, after B-ALL patients have been stratified into risk subgroups, a second informed consent that describes the next phase of their therapy will be discussed with patients and their families. There are separate post-Induction consents for children with LR B-ALL, AR B-ALL, and DS SR B-ALL. Patients with AR-subset of SR B-ALL will be approached with a third consent prior to beginning Maintenance therapy that describes the 2x2 randomization to 1 of 4 different Maintenance regimens.

For AR and LR B-ALL patients enrolled after accrual goals for AR patients have been met:
AR and LR B-ALL patients enrolled after accrual goals for AR patients have been met will not receive post-Induction treatment on AALL0932. However, upon completion of Induction therapy and risk group assignment, AR and LR patients will come off protocol therapy but those patients who are classified at end Induction to meet HR-DS, HR and VHR criteria may be eligible for enrollment onto AALL1131 after Induction.

Summary of Required Consents for AALL0932: Before Accrual Goals for AR Patients Have Been Met

	Time Point for Obtaining Consent	Population for Consent*
Induction Consent	Prior to the start of Induction	• All SR B-ALL non-Down syndrome patients or Down syndrome patients (non-randomized)
Post-Induction Consent	Prior to the start of Consolidation	• LR B-ALL (randomized)
		• AR B-ALL (non-randomized)
		• DS SR B-ALL (non-randomized)
Maintenance Consent	Prior to the start of Maintenance	• AR B-ALL (randomized)
Induction and post-Induction Consent	Prior to the start of Induction	• B-LLy and DS B-LLy (non-randomized)

* *Each of these groups will sign a separate consent at the designated time points*

Summary of Required Consents for AALL0932: After Accrual Goals for AR Patients Have Been Met

	Time Point for Obtaining Consent	Population for Consent*
Induction Consent	Prior to the start of Induction	• All SR B-ALL non-Down syndrome patients or Down syndrome patients (non-randomized)
Post-Induction Consent	Prior to the start of Consolidation	• DS SR B-ALL (non-randomized)
Induction and post-Induction Consent	Prior to the start of Induction	• B-LLy and DS B-LLy (non-randomized)

* *Each of these groups will sign a separate consent at the designated time points*

3.1.6 Bilingual Services

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

3.1.7 Callback for Treatment Assignment/Randomization

After sufficient AR patients have completed Callback 1 such that accrual goals for AR patients have been met, these patients will not receive post-Induction therapy on this study.

For patients enrolled before accrual goals for AR patients have been met:
There will be 2 Callback procedures performed during this study. The first Callback (Callback #1 – post-Induction/pre-Consolidation for all patients) is performed for all patients after completion of Induction therapy (and subsequent Risk Assignment for the B-ALL patients), and prior to beginning Consolidation therapy. Callback #1 will: (1) treatment assign remaining therapy for the DS SR B-ALL patients to Arm DS; (2) treatment assign post-Induction therapy through Interim Maintenance II for the AR B-ALL patients; and (3) randomly assign the LR B-ALL patients to either Arm LR-M or Arm LR-C; (4) treatment assign remaining therapy with Maintenance Arm LLy for the B-LLy patients; and (5) treatment assign remaining therapy with Maintenance Arm DS for the DS B-LLy patients. See experimental design schema.

The second Callback (Callback #2 – Maintenance therapy for AR B-ALL patients) is to be performed only for the AR B-ALL patients post-Interim Maintenance II therapy within 72 hours prior to the planned start of Maintenance therapy. Callback #2 will randomly assign these patients to either treatment Arm A, B, C, or D (see experimental design schema.)

For patients enrolled after accrual goals for AR patients have been met:
There will be no call back for LR, AR, HR and VHR B-ALL patients.

There will be 1 Callback procedure performed during this study. The Callback (Callback #1 – post-Induction/pre-Consolidation for DS SR B-ALL, DS B-LLy, and B-LLy patients) is performed after completion of Induction therapy, and prior to beginning Consolidation therapy. Callback #1 will assign remaining post-Induction therapy for the DS SR B-ALL and DS B-LLy patients to Arm DS; as well as non-DS B-LLy patients. See experimental design schema.

If you have problems with either Callback process, email a request for assistance to the COG Help Desk and copy the AALL0932 Research Coordinator.

B-ALL patients classified as AR or LR at the end of Induction will not be eligible for post-Induction therapy on this trial. Further treatment for these patients will be up to the discretion of the treating physician.

B-ALL patients classified as HR or VHR at the end of Induction will not be eligible for post-Induction therapy on this trial, but may be eligible for enrollment on the COG HR/VHR trial, AALL1131.

B-LLy or DS B-LLy patients with progressive disease (PD) at the end of Induction will not be eligible for post-Induction therapy on this trial.

3.1.7.1 LR B-ALL

LR B-ALL patients enrolled after accrual goals for AR patients have been met will not receive post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

For patients enrolled before accrual goals for AR patients have been met, randomization for post-Induction therapy for patients with LR subset of SR B-ALL is accomplished by completing the Callback in the RDE system, after the risk assignment has been completed and consent signed, and prior to the planned start of Consolidation therapy. Patients will be randomly assigned to either the Arm LR-M or Arm LR-C; see experimental design schema.

3.1.7.2 AR B-ALL

AR B-ALL patients enrolled after accrual goals have been met will not receive post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

Patients enrolled before accrual goals for AR patients have been met, who are risk-assigned to the AR subset of SR B-ALL will sign consent to 7 months of post-Induction/pre-Maintenance therapy prior to starting Consolidation. At this time, they will be treatment assigned to this pre-Maintenance therapy via the Callback application in the RDE system. They will then sign a third consent and be randomized to 1 of 4 Maintenance therapy regimens [Treatment Arm A, B, C or D (see experimental design schema)] at the end of Interim Maintenance II. Randomization for the AR B-ALL patients is accomplished by going to the Callback application in the RDE system for a second time within 72 hours prior to the planned start of Maintenance therapy. Effective 01/13/2017 all patients on Arms B or D are recommended to have their oral methotrexate dose lowered to 20 mg/m^2/week, the standard of care therapy. Subsequently, patients should have their doses of 6 mercaptopurine and methotrexate adjusted based on tolerability following normal dose escalation procedures, as outlined in the protocol Section 5.9.

3.1.7.3 DS SR B-ALL

Patients with DS SR B-ALL may consent to non-randomized post-Induction treatment, after risk assignment and prior to the beginning of Consolidation therapy. Treatment assignment for these patients is accomplished by going to the Callback application in the RDE system at the end of Induction but prior to the start of Consolidation.

3.1.7.4 B-LLy or DS B-LLy

Patients with B-LLy will be non-randomly assigned to post-Induction therapy similar to AR B-ALL with Maintenance "Arm LLy". Patients with DS B-LLy will be non-randomly assigned to post-Induction therapy same as for patients with DS SR B-ALL. Treatment assignment for these patients is accomplished by going to the Callback application in the RDE system at the end of Induction but prior to the start of Consolidation.

3.2 Patient Eligibility Criteria

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy 7.2). 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.**

INCLUSION CRITERIA

3.2.1 Classification study

B-ALL patients must be enrolled on AALL08B1 or APEC14B1 (*if open for the classification of newly diagnosed ALL patients*) prior to treatment and enrollment on AALL0932.

Please note: B-LLy patients are not eligible for AALL08B1, and can enroll directly onto AALL0932.

3.2.2 Age and WBC Criteria

3.2.2.1

Patients must be > 365 days and < 10 years of age (for B-ALL patients)
Patients must be > 365 days and ≤ 30.99 years of age (for B-LLy patients)

3.2.2.2

B-ALL patients must have an initial white blood cell count < 50,000/μL.

3.2.3 Diagnosis

Patients must have newly diagnosed NCI Standard Risk B-ALL or B-LLy Murphy Stages I or II (See Appendix V for staging). Patients with Down syndrome are also eligible.

Note: For B-LLy patients with tissue available for flow cytometry, the criterion for diagnosis should be analogous to B-ALL. For tissue processed by other means (i.e. paraffin blocks), the methodology and criteria for immunophenotypic analysis to establish the diagnosis of B-LLy defined by the submitting institution will be accepted.

EXCLUSION CRITERIA

3.2.4 Prior Therapy

With the exception of steroid pretreatment (defined below) or the administration of intrathecal cytarabine, patients must not have received any prior cytotoxic chemotherapy for either the current diagnosis of B-ALL or B-LLy or for any cancer diagnosed prior to initiation of protocol therapy on AALL0932.

Patients receiving prior steroid therapy may be eligible for AALL0932 as defined below (Section 3.3).

3.2.5 Patients with CNS3 leukemia (see definition in Section 3.3 below).

CNS status must be known prior to enrollment because NCI SR patients with CNS disease (CNS3) are not eligible for AALL0932 (but are eligible for the COG HR ALL protocol). (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 3.3.). B-LLy patients with CNS3 disease are not eligible for this protocol or the COG HR ALL protocol. It is recommended that intrathecal cytarabine be administered at the time of the diagnostic lumbar puncture. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. This is allowed prior to registration. **Systemic chemotherapy must begin within 72 hours of the first dose of intrathecal therapy.**

3.2.6 B-ALL patients with testicular leukemia are not eligible for AALL0932.

3.2.7 For B-LLy patients the following additional exclusion criteria apply:

- T-Lymphoblastic Lymphoma.
- Morphologically unclassifiable lymphoma.
- Absence of both B-cell and T-cell phenotype markers in a case submitted as lymphoblastic lymphoma.
- CNS3-positive disease (see Section 3.3 for details) or testicular involvement.
- M2 (5% - 25% blasts) or M3 (> 25% blasts) marrow.
- Female patients who are pregnant are ineligible since fetal toxicities and teratogenic effects have been noted for several of the study drugs.
- Lactating females are not eligible unless they have agreed not to breastfeed their infants.
- Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.
- Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation.

3.2.8 Eligibility Criteria for the Patient Leukemia Experience Study (see **Section 15.1.1**)

Closed to accrual as of April 19, 2013.

3.2.9 Eligibility Criteria for the Leukemia Physical Functioning Study (see **Section 16.1.1**)

Closed to accrual as of March 15, 2013.

REGULATORY

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

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

3.3 Definitions

INITIAL WBC: The first WBC at the treating COG institution, or the WBC prior to intravenous fluids, whichever occurred first. If prior therapy (i.e. steroids) has been administered and a CBC is available that was obtained within 72 hours prior to steroid therapy, then this pre-steroid WBC 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 FOR B-ALL PATIENTS:

1. For patients older than 10 years of age: the use of steroids prior to diagnosis will not affect their Induction therapy. Patients must meet all eligibility criteria (including an M3 bone marrow at diagnosis, or peripheral count of at least 1,000/μL leukemic blasts for patients in whom there is a medical contraindication to a bone marrow aspirate). Post-Induction risk assignment will be refined by leukemia specific genetic features and the level of bone marrow MRD at Day 29. (Note this definition applies only to children with NCI HR-ALL). (These patients are not eligible for this trial but may be eligible for the COG HR-ALL trial).

2. For patients younger than 10 years of age: If steroids are given for more than 24 hours in the 2 weeks prior to diagnosis and a CBC is obtained within 3 days prior to initiation of the steroid, the patient will be assigned to Induction based on NCI risk group using the pre-steroid WBC. Post-Induction risk assignment will be refined by leukemia-specific genetic features and the level of bone marrow MRD at Day 29, except that SR patients in this group will not be eligible for the LR arm of AALL0932. If there is no pre-steroid CBC obtained, the patient will be assigned to receive Induction therapy on the COG HR protocol AALL1131. These patients are not eligible for AALL0932 but may be eligible for AALL1131. If steroids are given for less than 24 hours in the 2 weeks prior to diagnosis, Induction risk group will be based on NCI risk group using the initial WBC and patients will not be eligible for the LR arm.

3. For patients younger than 10 years of age: Any amount of steroid pretreatment at any time prior to 2 weeks before diagnosis will not affect initial induction assignment as long as the patient meets all other eligibility criteria including the presence of an M3 marrow at diagnosis. The presenting WBC at the time of diagnosis will be used to assign the patient to SR or HR Induction therapy. Post-Induction risk assignment will be refined by leukemia-specific genetic features and the level of bone marrow MRD at Day 29. SR patients in this group may be eligible for the LR arm only if they did not receive steroids within the month prior to diagnosis.

4. Inhalational steroids are not considered as pretreatment.

STEROID PRETREATMENT FOR B-LLy PATIENTS:
Patients receiving steroids within 4 weeks of diagnosis:

1. Patients who have received ≤ 48 hours of oral or IV steroids will be eligible for AALL0932.
2. Patients who have received > 48 hours of oral or IV steroids, will not be eligible for AALL0932 because they cannot reasonably be classified as localized.

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 traumatic LP, ≥ 5/μL WBCs, cytospin positive for blasts, but negative by Steinherz/Bleyer algorithm:

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

CNS3: In CSF, after traumatic LP 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).

B-LLy DEFINITION OF CNS3 POSITIVE DISEASE:

CNS3: Elevated CSF WBC (≥ 5 cells/μL) and a cytocentrifuge preparation demonstrating lymphoblasts. CNS lymphoma may also be diagnosed when the CSF WBC is normal but clinical signs of CNS involvement are present:
- Cranial nerve palsy (if not explained by extra cranial tumor)
- Clinical spinal cord compression
- Isolated intracerebral mass

B-LLy PATIENTS WHO HAVE CNS3 DISEASE ARE NOT ELIGIBLE FOR THIS STUDY

METHOD OF EVALUATING INITIAL TRAUMATIC LUMBAR PUNCTURES:
If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/μL and blasts, the following Steinherz/Bleyer algorithm should be used to distinguished between CNS2 and CNS3 disease:

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

A patient with CSF WBC ≥ 5/μL blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC = 60/μL; CSF RBC = 1,500/μL; blood WBC = 46,000/μL; blood RBC = 3.0 X 10^6/μL:

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

TESTICULAR LEUKEMIA AT DIAGNOSIS:
Unilateral or bilateral testiculomegaly. Biopsy is required if clinical findings are equivocal or suggestive of hydrocele or a non-leukemic mass. These B-ALL patients are not eligible for this study, but may be eligible to enroll on the COG HR B-ALL study.

B-LLy PATIENTS WITH TESTICULAR INVOLVEMENT ARE NOT ELIGIBLE FOR THIS STUDY.

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

B-LLy PATIENTS WITH AN M2 OR M3 MARROW AT DIAGNOSIS ARE NOT ELIGIBLE FOR THIS STUDY.

BONE MARROW MRD STATUS (Day 29) FOR B-ALL PATIENTS:
Positive: ≥ 0.01% detectable leukemia cells
Negative: < 0.01% detectable leukemia cells

BONE MARROW MINIMAL MARROW DISEASE (MMD) STATUS FOR B-LLy PATIENTS:
The MMD status of B-LLy patients will be assessed at diagnosis for research purposes but not used for risk stratification. Closed effective Amendment #5.

UNFAVORABLE CHARACTERISTICS FOR B-ALL PATIENTS:
1. iAMP21 as identified by fluorescence in-situ hybridization (FISH).

2. *KMT2A (MLL)* rearrangements as identified by cytogenetics, fluorescence in-situ hybridization (FISH), or molecular studies.

3. HYPODIPLOIDY: Fewer than 44 chromosomes and/or DNA index < 0.81, or other clear evidence of a hypodiploid clone.

4. INDUCTION FAILURE:
   a) M3 marrow on Day 29.

Patients entered on AALL0932 who are later found to have 1 of the 4 above UNFAVORABLE CHARACTERISTICS will be eligible to enroll into the VHR arms of AALL1131 at end of Induction therapy; or otherwise will be off protocol therapy at the end of Induction therapy.

5. PHILADELPHIA CHROMOSOME POSITIVE (Ph+) ALL:
   a) *BCR-ABL1* (formerly known as *BCR-ABL*) fusion transcript determined by FISH or RT-PCR
   b) t(9;22)(q34;q11) determined by cytogenetics

Patients enrolled on AALL0932 who are later found to have Ph+ ALL and meet eligibility criteria for the AALL1122 (successor COG Ph+ ALL trial) should be immediately taken off protocol therapy prior to Day 15 of Induction therapy if eligible to enroll on AALL1122 (or its successor COG Ph+ ALL trial). Otherwise, Ph+ ALL patients may continue on AALL0932 until the end of Induction therapy.

RELAPSE (B-ALL PATIENTS):
Any recurrence of disease whether in marrow or extramedullary. Relapse should be biopsy confirmed.

1) ISOLATED BONE MARROW RELAPSE:
Patients with an M3 marrow at any point after achieving remission without involvement of the CNS and/or testicles.

2) COMBINED RELAPSE:
M2 or M3 marrow at any point after achieving remission with concomitant CNS and/or testicular relapse.

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

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

RELAPSE/PROGRESSIVE DISEASE (PD): B-LLy PATIENTS:
Greater than 50% increase in the size of any lesions or appearance of new lesion(s) more than 1.5 cm in any axis.

DISEASE EVALUATION DURING FOLLOW-UP:
A disease evaluation is a procedure ordered with the intent to measure or assess the disease status of a patient. The most common evaluations are a bone marrow aspirate and/or biopsy and a lumbar puncture (LP). If a CBC has findings that raise suspicion for relapse, a bone marrow aspirate must be performed to confirm the relapse.

POST INDUCTION RISK GROUPS FOR B-ALL PATIENTS

LOW RISK B-ALL CRITERIA
NCI standard risk (age 1.01 - 9.99 years and initial WBC < 50,000/μL) B-ALL and all of the following:

a. Favorable genetics: the presence of simultaneous trisomies of chromosome 4 and 10 (double trisomy; DT) or *ETV6/RUNX1* fusion
b. Day 8 PB MRD less than 0.01%
c. Day 29 BM MRD less than 0.01%
d. No CNS2, CNS3 or testicular leukemia
e. No steroid pretreatment
f. No Down syndrome
g. No unfavorable genetic characteristics.

AVERAGE RISK B-ALL CRITERIA:
NCI standard risk (age 1.01 - 9.99 years and initial WBC < 50,000/μL) B-ALL and:

a. Favorable genetics: the presence of DT or *ETV6/RUNX1* fusion
b. Day 8 PB MRD ≥ 0.01% or CNS2 status
c. Day 29 BM MRD less than 0.01%
d. No CNS3 or testicular leukemia
e. No Down syndrome
f. No unfavorable genetic characteristics.

OR,

NCI standard risk (age 1.01 - 9.99 years and initial WBC < 50,000/μL) B-ALL and:

a. Neither favorable nor unfavorable cytogenetics
b. Day 8 PB MRD less than 1%
c. Day 29 BM MRD less than 0.01%
d. No CNS3 or testicular leukemia
e. No Down syndrome

STANDARD RISK DS B-ALL CRITERIA

NCI standard risk (age 1.01 - 9.99 years and initial WBC < 50,000/μL) DS B-ALL and:

a. No *KMT2A* (*MLL*)-rearrangement, hypodiploidy, or Philadelphia chromosome
b. Day 29 BM MRD less than 0.01%
c. No CNS3 or testicular leukemia

Note: DS B-ALL patients who have Day 29 BM MRD ≥ 0.01% will be eligible for post-Induction therapy on the DS stratum of the HR trial.

For an overview of the classification system for B-ALL, see AALL08B1 or the APEC14B1 (*if open for classification of newly diagnosed ALL patients*) ALL manual of procedures (MOP).

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 of Treatment Plan

Informed consent that describes the first 4 weeks of Induction therapy for B-ALL is required. **After sufficient AR patients have completed Callback 1 such that accrual goals for AR patients have been met, AR and LR B-ALL patients will not receive post-Induction treatment on AALL0932 and will come off protocol therapy after Induction. Further treatment for these patients will be up to the discretion of the treating physician. HR and VHR patients may be eligible for enrollment onto AALL1131 after Induction.**

At the end of Induction, after patients have been stratified into risk subgroups, a second informed consent that describes the next portions of therapy must be signed prior to the start of Consolidation. This second consent will include randomized assignment to P9904 regimen A-based (Arm LR-M) or CCG 1991 regimen IS-based (with every 12 week vincristine/dexamethasone pulses during Maintenance; Arm LR-C) post-Induction therapy for LR patients enrolled before accrual goals for AR patients have been met. The second consent for DS SR B-ALL patients or AR B-ALL patients (enrolled before accrual goals for AR patients have been met) will not include randomized treatment assignment. Patients with AR B-ALL enrolled before accrual goals for AR patients have been met, will be approached with a third consent prior to beginning Maintenance therapy that describes the randomization to 1 of 4 different Maintenance arms. Effective 01/13/2017 all patients on Arms B and D were recommended to have their oral methotrexate dose lowered to 20 mg/m^2/week, the standard of care therapy. Subsequently, patients should have their doses of 6 mercaptopurine and methotrexate adjusted based on tolerability following normal dose escalation procedures, as outlined in the protocol Section 5.9. B-LLy and DS B-LLy patients will sign one consent form that describes all therapy to be received on study, prior to beginning Induction therapy.

Revised eligibility includes newly diagnosed patients, ages 1.0 to 30.99 years, with localized B-LLy. Patients with testicular involvement or CNS3 disease are not eligible. Down syndrome B-LLy patients are eligible and follow the treatment guidelines for Down syndrome B-ALL patients. Patients with Stages I and II B-LLy (without Down syndrome) will be non-randomly assigned to post-Induction therapy similar to the standard arm for Average Risk B-ALL with Maintenance "Arm LLy" on AALL0932.

CNS status must be known prior to enrollment because patients with CNS3 disease are not eligible for AALL0932 but patients with CNS3 B-ALL may be eligible for the COG HR B-ALL protocol. It is recommended that intrathecal cytarabine be administered at the time of the diagnostic lumbar puncture. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a 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 3.3.) This is allowed prior to registration. **Systemic chemotherapy must begin within 72 hours of this intrathecal therapy.** B-LLy patients with CNS3-positive and/or testicular disease are not eligible for this study.

NOTE: FOR NON-DS B-ALL PATIENTS, IF DAY 8 PB AND DAY 29 BM MRD SAMPLES ARE NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

4.1.1 Induction Therapy for B-ALL Patients

All patients will receive a common 3 drug dexamethasone based Induction identical to that on CCG 1991 and COG AALL0331 with the exception of intravenous rather than intramuscular administration of pegaspargase. Patients with DS SR B-ALL will also receive leucovorin rescue after IT MTX. At the end of Induction, patients will be further classified into risk categories. Those classified as DS SR B-ALL as defined by the classification study AALL08B1 or APEC14B1 (see Section 3.3) will be eligible for post-Induction therapy **on AALL0932.** Patients classified as LR B-ALL or AR B-ALL as defined by the classification study AALL08B1, who enrolled before accrual goals for AR patients have been met will be eligible for post-Induction treatment on AALL0932. Patients classified as LR B-ALL or AR B-ALL enrolled after accrual goals for AR patients have been met will not be eligible for post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

Those patients classified as HR or VHR based on the Induction MRD responses or adverse cytogenetic features are not eligible for post-Induction therapy on AALL0932, but may be eligible to receive post-Induction therapy on the COG HR- or VHR B-ALL protocols. See Section 7.1 for baseline studies to be obtained prior to starting Induction therapy.

Questions regarding Induction therapy should be directed to Dr. Anne Angiolillo and Dr. Reuven Schore.

4.1.2 Post Induction Therapy (Pre-Maintenance) for B-ALL Patients (enrolled before accrual goals for AR patients have been met)

Average Risk

AR B-ALL patients enrolled after accrual goals have been met will not receive post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

The AR subset of SR B-ALL patients must consent prior to starting Consolidation therapy to receive 7 months of therapy identical to the IS-arm of CCG 1991: Consolidation, 2 Interim Maintenance phases with vincristine and escalating IV methotrexate, and 1 Delayed Intensification phase. Patients will then be approached with a third consent at the end of IM II that describes randomization to 1 of 4 Maintenance treatment arms.

Questions regarding the Average Risk patients should first be directed to Dr. Anne Angiolillo.

Low Risk

LR B-ALL patients enrolled after accrual goals for AR patients have been met will not receive post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

The LR subset of SR B-ALL group must consent prior to starting Consolidation therapy to be randomized to receive either (a) Consolidation therapy identical to that on Regimen A of COG P9904 with the exception that oral 6-MP in Consolidation will start 1 week later to allow time for the end-Induction risk assignment (Arm LR-M); or (b) therapy identical to that for AR patients with reduced vincristine/dexamethasone pulses at 12-week intervals during Maintenance (Arm LR-C).

Questions regarding the Low Risk patients should first be directed to Dr. Reuven Schore.

DS SR B-ALL

The DS SR B-ALL group will receive modified Induction and post-Induction therapy due to the higher risk of treatment-related morbidity and mortality and will not be included in the randomized questions addressed in Maintenance therapy for SR B-ALL patients without Down syndrome. At the end of Induction therapy, children with DS SR B-ALL must consent prior to starting Consolidation therapy to receive therapy identical to the IS-arm of CCG 1991 with the following modifications: (1) Leucovorin rescue will be given following intrathecal methotrexate in all phases prior to Maintenance; (2) Maintenance vincristine/dexamethasone pulses will be given every 12 weeks; (3) Maintenance duration will be 2 years from the start of IM I for both boys and girls.

Questions regarding the Down syndrome patients should first be directed to Dr. Johann Hitzler.

4.1.3 Post Induction Therapy (Maintenance) for B-ALL Patients (enrolled before accrual goals for AR patients have been met)

Average Risk- Patients randomized prior to June 15, 2015

AR B-ALL patients enrolled after accrual goals have been met will not receive post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

The AR subset of SR B-ALL patients will be randomized to 1 of 4 Maintenance treatment arms at the end of IM II:

i.) **Arm A**- vincristine/dexamethasone pulses at 4 week intervals, intrathecal methotrexate every 12 weeks and oral methotrexate at dose 20 mg/m^2/week.

ii.) **Arm B**- vincristine/dexamethasone pulses at 4 week intervals, intrathecal methotrexate every 12 weeks and oral methotrexate at dose 40 mg/m^2/week.

iii.) **Arm C**-vincristine/dexamethasone pulses at 12 week intervals, intrathecal methotrexate every 12 weeks and oral methotrexate at dose 20 mg/m^2/week.

iv.) **Arm D**-vincristine/dexamethasone pulses at 12 week intervals, intrathecal methotrexate every 12 weeks and oral methotrexate at dose 40 mg/m^2/week.

Effective the memo dated 01/13/2017 all patients on Arms B and D were recommended to have their oral methotrexate dose lowered to 20 mg/m^2/week, the standard of care therapy. Subsequently, patients should have their doses of 6 mercaptopurine and methotrexate adjusted based on tolerability following normal dose escalation procedures, as outlined in the protocol Section 5.9.

Questions regarding the Average Risk patients should first be directed to Dr. Anne Angiolillo.

Low Risk

LR B-ALL patients enrolled after accrual goals for AR patients have been met will not receive post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

The LR subset of SR B-ALL patients will have been randomly assigned to either:

i.) **Arm LR-M -** vincristine/dexamethasone pulses at 16-week intervals, intrathecal methotrexate every 12 weeks (until completion of 8 doses) and oral methotrexate at dose 20 mg/m^2/week.

Maintenance therapy starts at the end of Consolidation and is based on Regimen A of COG P9904.

ii.) **Arm LR-C** - vincristine/dexamethasone pulses at 12-week intervals, intrathecal methotrexate every 12 weeks and oral methotrexate at dose 20 mg/m^2/week.

Questions regarding the Low Risk patients should first be directed to Dr. Reuven Schore.

DS SR B-ALL

DS SR B-ALL patients will be non-randomly assigned the **Arm DS** Maintenance arms.

4.1.4 Induction and Post-Induction Therapy for B-LLy and DS B-LLy Patients

All B-LLy patients will receive a common 3-drug dexamethasone-based Induction with intravenous rather than intramuscular administration of pegaspargase. B-LLy patients without progressive disease at end-Induction will be non-randomly assigned to post-Induction therapy similar to AR B-ALL with a modified Maintenance (Arm LLy), to receive 7 months of therapy identical to the IS-arm of CCG 1991: Consolidation, 2 IM phases with vincristine and escalating IV methotrexate, and 1 DI phase followed by a modified standard Maintenance (**Arm LLy**). Modified Standard Maintenance will comprise vincristine/dexamethasone pulses at 4-week intervals and a weekly oral methotrexate dose of 20 mg/m^2 and the following modification:

- Total treatment length for girls AND boys will be 2 years from the start of IM I.

DS B-LLy patients will receive a modified Induction and post-Induction therapy same as for patients with DS SR B-ALL due to the higher risk of treatment-related morbidity and mortality. Following Induction, DS B-LLy patients without progressive disease will be non-randomly assigned to post-Induction therapy same as for patients with DS SR B-ALL, to receive 7 months of therapy identical to the IS-arm of CCG 1991: Consolidation, 2 IM phases with vincristine and escalating IV methotrexate, and 1 DI phase followed by Maintenance (**Arm DS**). The modifications to the therapy for patients with DS B-LLy are:

- Leucovorin rescue will be given following intrathecal methotrexate in all phases prior to Maintenance.
- Maintenance vincristine/dexamethasone pulses will be given every 12 weeks.
- Maintenance duration will be 2 years from the start of IM I for both boys and girls.

Questions regarding the B-LLy or DS B-LLy patients should first be directed to Dr. Birte Wistinghausen.

4.1.5 Duration of Therapy

Average Risk

AR B-ALL patients enrolled after accrual goals have been met will not receive post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

The duration of Maintenance therapy will continue to be gender based for patients with AR subset of SR B-ALL: 2 years from the start of Interim Maintenance I for female patients and 3 years from the start of Interim Maintenance I for male patients.

Questions regarding the Average Risk patients should first be directed to Dr. Anne Angiolillo.

Low Risk

LR B-ALL patients enrolled after accrual goals for AR patients have been met will not receive post-Induction treatment on AALL0932. Further treatment for these patients will be up to the discretion of the treating physician.

For LR subset of SR B-ALL patients assigned to Arm LR-M, the duration of therapy will be 2½ years from diagnosis for both female and male patients. For those assigned to Arm LR-C, the duration of therapy will continue to be gender based: 2 years from the start of Interim Maintenance I for female patients and 3 years from the start of Interim Maintenance I for male patients.

Questions regarding the Low Risk patients should first be directed to Dr. Reuven Schore.

DS B-ALL

For DS SR B-ALL patients, duration of Maintenance therapy will not be gender based; instead both female and male patients will receive 2 years from the start of Interim Maintenance I.

Questions regarding the Down syndrome patients should first be directed to Dr. Johann Hitzler.

B-LLy and DS B-LLy

The duration of Maintenance therapy will not be gender based and will be 2 years from the start of IM I for both boys and girls.

Questions regarding the B-LLy or DS B-LLy patients should first be directed to Dr. Birte Wistinghausen.

4.1.6 HRQOL Ancillary Studies (B-ALL Patients ONLY).

Both HRQOL ancillary studies are closed to new patient enrollment due to accrual goals being met. Closure to accrual occurred on March 3, 2013 for the LPFS study and April 19, 2013 for the PLES study.

Institutions are required to continue data collection at remaining evaluation time points for patients already enrolled on this study.

These patients will have additional required observations during Consolidation and Maintenance. For further instructions on timing and specific tests to be administered see Sections 15.0 & 16.0.

Questions regarding the HRQOL surveys should be directed to Dr. Nina Kadan-Lottick.

4.2 Induction (35 days) – B-ALL and B-LLy Patients

All patients without DS will receive common Induction therapy. For patients with Down syndrome see Section 4.20.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cytarabine: Intrathecal (IT)

All patients: Given at the time of diagnostic lumbar puncture (LP) OR on Day 1. May be given up to 72 hours prior to the start of protocol therapy for patient convenience.

Age-based dosing for Day 1 IT Cytarabine:

Age (yrs)	Dose
1 – 1.99	30 mg
2 – 2.99	50 mg
≥ 3	70 mg

B-ALL CNS2 patients ONLY: In addition to the initial dose (above), patients will receive additional IT Cytarabine on either Day 4, 5 or 6 during Induction, IT Methotrexate on Day 8, and then receive IT Cytarabine on Days 11 or 12. If the CSF at all three of these time points is negative for blasts, patients will receive their next IT therapy with methotrexate on Day 29. If the CSF remains positive after the initial LP, patients will continue IT Cytarabine twice weekly during Induction until the CSF is clear for three consecutive LPs. All patients will receive IT therapy with methotrexate on Day 8 and 29 at the end of Induction regardless of CSF evaluations.

Age-based dosing for additional IT Cytarabine for **B-ALL CNS2 patients ONLY (Days 4, 5 or 6 and Days 11 or 12) and additional IT** Cytarabine until clear:

Age (yrs)	Dose
1 – 1.99	20 mg
2 – 2.99	30 mg
≥ 3	40 mg

For IT administration use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

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

Days 1, 8, 15 and 22

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

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (may be given IV)
Days 1 - 28 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)
Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/day, divided BID) may be used temporarily as needed.

Pegaspargase: IV over 1 - 2 hours
Day 4*
Dose: 2,500 International Units/m^2/dose

Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

***PLEASE NOTE: FOR B-ALL PATIENTS, DUE TO THE IMPORTANCE OF DAY 8 EARLY RESPONSE ASSESSMENT, PEGASPARGASE SHOULD BE ADMINISTERED ON DAY 4**. Deviation from Day 4 administration may adversely impact risk categorization.

Special precautions:

1. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
2. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Methotrexate: Intrathecal (IT)
Days 8 and 29
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Disease Evaluations During Induction for B-ALL Patients:

- Day 8: 5 mL of peripheral blood will be obtained and shipped to a COG-Approved ALL Flow Cytometry Laboratory for MRD determination. **Day 8 PB sample must be collected prior to administration of Day 8 IV/IT chemotherapy.**
- Day 29: Bone marrow sample will be obtained for morphology and a 2 mL aliquot will be shipped to a COG-Approved ALL Flow Cytometry Laboratory for MRD determination.

Research Studies (for B-ALL patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (*if available for classification of newly diagnosed ALL patients*))

- Day 29: 5 mL of peripheral blood will be obtained and shipped to the COG ALL Molecular Reference Laboratory for studies of genomic variation and cell banking. ***This specimen is very important and should be obtained on all patients that have provided consent.***

NOTE: FOR NON-DS B-ALL PATIENTS, IF DAY 8 PB AND 29 BM MRD SAMPLES ARE NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

Disease Evaluation for B-LLy Patients:

- Before starting therapy and on Day 29: patients will have a CT of the neck, chest, abdomen and pelvis, CXR, a PET scan, and if indicated a bone scan (please refer to Section 7.1d for details).

Note: A PET scan is highly recommended but not required at diagnosis, at the end of Induction and if there are residual masses at the end of Consolidation.

Optional Research Studies for B-LLy Patients (see Section 14.0 for details)**:**

- If patient consents, paraffin embedded tissue will be submitted at diagnosis for FISH analysis.
- If patient consents, fresh tissue will be submitted at diagnosis for banking.
- Day 29: 5 mL of peripheral blood will be obtained and shipped to the COG ALL Molecular Reference Laboratory for studies of genomic variation. ***This specimen is very important and should be obtained on all patients that have provided consent.***

SEE SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE GUIDELINES.

Following completion of Induction, based upon the patient's Day 29 MRD results, B-ALL patients will be classified as AR B-ALL or LR B-ALL:

For AR B-ALL patients **enrolled before accrual goals for AR patients have been met**: Consolidation (Section 4.3) starts on Day 36 or when blood count parameters are met (whichever occurs later)

For LR B-ALL patients **enrolled before accrual goals for AR patients have been met**: For LR patients randomized to Arm LR-C, Consolidation (Section 4.3) starts on Day 36 or when blood count parameters are met (whichever occurs later). For LR patients randomized to Arm LR-M, Consolidation (Section 4.12) starts on Day 36 regardless of blood count parameters.

Following completion of Induction, only B-LLy patients without PD (see Section 11.3 for definition) will be eligible to continue Consolidation therapy. **B-LLy patients with PD at end-Induction will be**

considered off protocol therapy. Consolidation (Section 4.3) starts on Day 36 or when blood count parameters are met (whichever occurs later).

The therapy delivery maps (TDMs) for Induction are on the next two (2) pages. For B-ALL patients see Section 4.2.1 and for B-LLy patients see Section 4.2.2.

4.2.1 Induction (35 days).- B-ALL Patients

All patients without DS receive common Induction Therapy.

For patients with Down syndrome see Section 4.20.

Patient name or initials _____ DOB _____

Induction therapy lasts 5 weeks (35 days). See Section 4.1 for full details regarding assignment to treatment arms and subsequent therapy. This Therapy Delivery Map is on one (1) page

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Cytarabine (IT ARAC)	IT	Age (yrs) Dose 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg	Given at time of diagnostic LP OR Day 1*	See Section 4.2 for administration guidelines **Note age-based dosing**	a. Hx, PE, Wt, Ht b. CBC/diff/platelets c. BM eval[1] d. PB sample[1] e. CSF cell count, cytospin[2] f. Creatinine, Bili, Albumin & ALT g. Varicella titer h. TPMT and NUDT15 genotype[#] [1]See Section 7.1 for details [2] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Cytarabine (IT ARAC)	IT	CNS2 patients ONLY Age (yrs) Dose 1-1.99 20 mg 2-2.99 30 mg ≥ 3 40 mg	**CNS2:** twice weekly[†]	[†] The initial dose is followed by twice weekly IT ARAC except during weeks when Days 8 & 29 IT MTX is administered **Note:** IT therapy is administered until 3 consecutive CSF samples are clear of blasts.	
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m^2/dose	Days 1, 8, 15 &22	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX)	PO (may give IV)	3 mg/m^2/dose BID	Days 1-28 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.2 for administration guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4	**Note: pegaspargase should be administered on Day 4.** Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 8 and 29	See Section 4.2 for administration guidelines **Note age-based dosing** **Note:** All patients receive Day 8 and 29 IT MTX regardless of CSF evaluation.	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	IT ARAC ____mg	IT ARAC ____mg	VCR ____mg	DEX (BID dosing) ____mg ____mg	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
				Enter calculated dose above and actual dose administered below						
			_____mg						(a[%]-c, e-g)[@]	
		-2/-1/0/LP*								
		1			_____mg	__mg __mg				
		2								
		3								
		4[♦]		_____mg[♦]			_____IU		e[♦]	

		8			_____mg			____mg	a[%], b, d**, e	
		9								

		11[♦]		_____mg[♦]					e[♦]	

		15			_____mg				a[%], b, h	

		22			_____mg				a[%], b	

		28								
		29						____mg	a[%], b, c**, d***, e	

		35								
		36		Begin Consolidation (Section 4.3) for AR B-ALL (without PD) or LR B-ALL patients randomized to Arm LR-C on Day 36 or when blood count parameters have been met (whichever occurs later). Begin Consolidation (Section 4.12) for LR B-ALL patients randomized to Arm LR-M on Day 36 regardless of blood counts.						

*On Day 1 **OR** at the time of diagnostic lumbar puncture (LP) if ≤ 72 hours from the start of protocol therapy. [@]Baseline

[♦]**CNS2 patients only: administer IT therapy twice weekly until 3 consecutive CSF are clear of blasts. Day 8 & 29 IT therapy will remain IT MTX for all patients.**

Note: CNS2 patients receive IT ARAC on Days 4, 5, or 6 and 11 or 12, etc., depending on treatment schedule. Log additional IT-ARAC doses in the comments section.

** **Note:** For B-ALL patients, if Day 8 PB and 29 BM MRD samples are not obtained and shipped to a COG Approved ALL flow cytometry laboratory, then the patient will not be eligible to continue on a COG ALL trial following completion of Induction therapy. **Day 8 PB sample must be collected prior to Day 8 IV/IT chemotherapy.**

*** Day 29 PB specimen should be shipped to the COG ALL Molecular Reference Laboratory for all B-ALL patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (if open for classification of ALL patients) (see Section 14.0 for specimen shipping and handling). ***This specimen is very important***.

[%] **Note**: Height (Ht) is only required at the beginning of this course.

[#] TPMT and NUDT15 genotype (TPMT highly recommended for all subjects; NUDT15 is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects (See Section 5.9)

DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL B-ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY.

SEE SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE GUIDELINES.

4.2.2 Induction (35 days).- B-LLy Patients

All patients without DS receive common Induction Therapy.

For patients with Down syndrome see Section 4.20.

_____ Patient name or initials

_____ DOB

Induction therapy lasts 5 weeks (35 days). See Section 4.1 for full details regarding assignment to treatment arms and subsequent therapy. This Therapy Delivery Map is on one (1) page

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Cytarabine (IT ARAC)	IT	Age (yrs) Dose 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg	Given at time of diagnostic LP OR Day 1	See Section 4.2 for administration guidelines **Note age-based dosing**.	a. Hx, PE, Wt,Ht b. CBC/diff/platelets c. BM eval[1] d. PB sample[1] e. CSF cell count, cytospin[2] f. Creatinine, Bili, Albumin & ALT g. Varicella titer h. TPMT and NUDT15 genotype[#] i. CT (neck, chest, abdomen & pelvis), CXR, PET, bone scan (if bone involvement). [3] j. Diagnostic biopsy/cytology [3] k. Biology/banking (optional) [4] [1]See Section 7.1 for details [2] Obtain with each IT administration [3] See Section 7.1d for details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m^2/dose	Days 1, 8, 15 &22	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX)	PO (may give IV)	3 mg/m^2/dose BID	Days 1-28 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.2 for administration guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4	**Note: pegaspargase should be administered on Day 4.** Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 8 and 29	See Section 4.2 for administration guidelines **Note age-based dosing**	

Ht ____ cm Wt ____ kg BSA ____ m^2

Date Due	Date Given	Day	IT ARAC ____ mg	VCR ____ mg	DEX (BID dosing) __ mg __ mg	PEG-ASP ____ IU	IT MTX ____ mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
								(a[%]-c, e-g, i-k)[@]	
		-2/-1/0/LP*	_____mg						
		1		_____mg	__mg __mg				
		2							
		3							
		4				_____IU			

		8		_____mg			____mg	a[%], b, e	
		9							

		15		_____mg				a[%], b, h	

		22		_____mg				a[%], b	

		28							
		29					____mg	a[%], b, d***, e, i	

		35							
		36	Begin Consolidation (Section 4.3) for B-LLy patients (without PD) on Day 36 or when blood count parameters have been met (whichever occurs later). **Note: B-LLy patients with PD at end-Induction are off protocol therapy.**						

* On Day 1 **OR** at the time of diagnostic lumbar puncture (LP) if ≤ 72 hours from the start of protocol therapy.

@ Baseline

*** Day 29 PB specimen should be shipped to the COG ALL Molecular Reference Laboratory for all B-LLy patients that consent on AALL0932 (see Section 14.0 for specimen shipping and handling). ***This specimen is very important***.

% **Note**: Height (Ht) is only required at the beginning of this course.

Note: PET scans are highly recommended, not required, and CXR is not required if CT chest is done.

TPMT and NUDT15 genotype (TPMT highly recommended for all subjects; NUDT15 is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects (See Section 5.9)

DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL B-LLY PATIENTS WHO DO NOT GO OFF PROTOCOL THERAPY AT END-INDUCTION.

SEE SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE GUIDELINES.

4.3 Consolidation (28 days) – AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C and B-LLy Patients

NOTE FOR B-ALL PATIENTS: AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

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

FOR PATIENTS WITH B-LLy: DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO DO NOT GO OFF PROTOCOL THERAPY AT THE END OF INDUCTION.

Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75 000/μL (whichever occurs later) after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Therapy should be interrupted for patients with suspected or proven serious infection and resumed when the signs of infection have abated. Therapy should not be interrupted for fever, if there are no signs of serious infection.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1 ONLY
Dose: 1.5 mg/m^2/dose (maximum 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Mercaptopurine: PO
Days 1 - 28
Dose: 75 mg/m^2/dose once daily *

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. Do not escalate dose based on blood counts during this cycle (see Section 5.8).

Methotrexate: Intrathecal (IT)
Days 1, 8, and 15Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

HRQOL Studies (B-ALL patients only)
The LFPS and PLES have met accrual goals and are closed to new patient enrollment as of March 15, 2013 and April 19, 2013, respectively. However, institutions are required to continue data collection at remaining evaluation time points, for patients already enrolled on this study.

Please note:
For AR B-ALL patients enrolled on the optional Patient Leukemia Experience Study (available at all centers) the first evaluation time point can occur anytime after Day 15 of Consolidation and prior to the start of Interim Maintenance I. For AR B-ALL patients enrolled on the Leukemia Physical Functioning Study (at selected sites only-available on the COG AALL0932 protocol webpage), the first evaluation time point can occur anytime after Day 15 of Consolidation and prior to the start of Interim Maintenance I. See Sections 15.0 & 16.0 for details of evaluation schedules.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

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

For B-ALL and B-LLy patients: Following completion of Consolidation, the next course (Interim Maintenance I, Section 4.4) starts on Day 29 or when blood count parameters are met (whichever occurs later).

Note: Following completion of Consolidation, B-LLy patients who fail to achieve CR (see Section 11.3 for definitions), are off protocol therapy with the exception of B-LLy patients with bone primaries who will be considered CR if there is resolution of all surrounding soft tissue component by the end of Consolidation.

4.3.1 Consolidation (28 days) – AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C and B-LLy Patients

_____
Patient name or initials

_____
DOB

Consolidation is 4 weeks (28 days). Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). See Section 4.3 for detailed therapy guidelines. This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Day 1 ONLY	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt , Ht b. CBC/diff/platelets c. CSF cell count, cytospin[1] d. Bilirubin, ALT & Creatinine e. Patient Leukemia Experience surveys[2] f. Leukemia Physical Functioning Study evaluation[2] **B-LLy patients only** g CT (neck, chest, abdomen & pelvis), CXR, PET, bone scan (if bone involvement). [1] Obtain with each IT administration [2] For AR B-ALL patients already enrolled on these ancillary studies; evaluations can be done any time from Day 15-29 (see Sections 15.0 & 16.0 for details). **Note**: B-LLy patients are not eligible for this study. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mercaptopurine (MP)	PO	75 mg/m^2/dose*	Days 1-28	See Section 4.3 & Appendix I for administration guidelines. * For suggested dose based on TPMT and NUDT15 status, see Section 5.9	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1, 8 & 15	See Section 4.3 for administration guidelines **Note age-based dosing**	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	VCR _____mg	MP _____mg	IT MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	_____mg	_____mg	_____mg	a, b, c, d	
		--		↓			
		8			_____mg	c	
		--					
		15			_____mg	c, e, f	
		--					
		22					
		--					
		28				g^	
		29	**Begin next course (Interim Maintenance I, Section 4.4) on Day 29 or when blood count parameters are met (whichever occurs later)** **Note: B-LLy patients without CR at end-Consolidation are off protocol therapy, except patients with bone primaries who are considered CR if there is resolution of all surrounding soft tissue component by the end of Consolidation.**				

^ For B-LLy patients ONLY. See Section 7.1d for details and exceptions. **Note**: PET scans for residual masses are highly recommended, not required and CXR is not required if CT chest is done.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.4 Interim Maintenance I (56 days) – AR B-ALL Patients, LR Patients Randomized to Arm LR-C, and B-LLy Patients

NOTE FOR B-ALL PATIENTS: AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Criteria to Start Interim Maintenance I

Begin IM I on Day 29 of Consolidation or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later.

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

A) If ANC is < 500/µL or platelets < 50,000/µL, hold all chemotherapy and repeat blood counts in 4 days.
    1. In 4 days, if ANC ≥ 500/µL and platelets ≥ 50,000/µL, give same dose of methotrexate as previously.
    2. In 4 days, if ANC is still < 500/µL or platelets < 50,000/µL, give VCR (and IT MTX if Day 31) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and IV MTX if counts are adequate.
        a) If after 7 days, ANC ≥ 500/µL and platelets ≥ 50,000/µL reduce dose of MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A-C.
        b) If after 7 days ANC is still < 500/µL or platelets < 50,000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL. When ANC ≥ 500/µL and platelets ≥ 50,000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A - C.
B) If ANC ≥ 500/µL but < 750/µL and/or platelets ≥ 50,000/µL but < 75,000/µL, give same dose of MTX as previously (i.e. no escalation).
C) If ANC ≥ 750/µL and platelets ≥ 75 000/µL escalate MTX by 50 mg/m^2/dose.
D) Do not escalate MTX dose and resume at 80% of last dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume escalation as per A-C.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

Days 1, 11, 21, 31, and 41

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

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Methotrexate: IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted).
Days 1, 11, 21, 31 and 41
Starting dose of 100 mg/m^2/dose; **thereafter, escalate by 50 mg/m^2/dose**

Methotrexate: Intrathecal (IT)
Day 31 ONLY
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Interim Maintenance I is on the next page.

For B-ALL and B-LLy patients: Following completion of Interim Maintenance I, the next course (Delayed Intensification, Section 4.5) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.4.1 **Interim Maintenance I (56 days) – AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C, and B-LLy Patients**	_____ Patient name or initials _____ DOB

Interim Maintenance I begins when ANC ≥ 750/µL and platelets ≥ 75,000/µL. This course lasts 8 weeks (56 days) and this Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF, cell count, cytospin[1] d. Bilirubin, ALT & Creatinine. **B-LLy patients only** e. CT (neck, chest, abdomen & pelvis), CXR, bone scan (if bone involvement). [1] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	IV over 2-5 min (undiluted) or 10-15 min (diluted)	Starting dose 100 mg/m^2 **& escalate by 50 mg/m^2/dose**	Days 1, 11, 21, 31 & 41	See Section 4.4 for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 31 ONLY	See Section 4.4 for administration guidelines **Note age-based dosing**	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	VCR ____mg	IV MTX ____mg *(escalating dose)*	IT MTX ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual administered dose below				
		1	____mg	____mg		a%, b, d	

		11	____mg	____mg		a%, b, d	

		21	____mg	____mg		a%, b, d	

		31	____mg	____mg	____mg	a%, b, c, d	

		41	____mg	____mg		a%, b, d	

		56				e^	
		57	**Begin next course (Delayed Intensification, Section 4.5) on Day 57 or when blood count parameters are met (whichever occurs later).**				

^ For B-LLy patients ONLY. **Note**: CXR is not required if CT chest is done .See Section 7.1d for details.

% **Note**: Height (Ht) is only required at the beginning of this course.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.5 Delayed Intensification (56 days) - AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C, and B-LLy Patients

NOTE FOR B-ALL PATIENTS: AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Criteria to Start Delayed Intensification

Delayed Intensification begins on Day 57 of Interim Maintenance I, or when ANC ≥ 750/μL and platelets ≥ 75,000/μL, whichever occurs later.

Interruption and/or Modifications of Therapy

All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 1 - 28 or Days 30 - 43, but Day 29 does not begin until ANC ≥ 750/μL and platelets ≥ 75,000/μL. Therapy interruptions should be made-up. In case of delays of 3 weeks or longer, notify the Study Chair.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Dexamethasone: PO (may give IV)

All patients, receive discontinuous dexamethasone therapy.
Days 1 - 7 and 15 - 21
Dose: 5 mg/m^2/dose BID (i.e., total daily dose: 10 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m^2/day, divided BID) may be used temporarily as needed.

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

Days 1, 8 and 15
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

DOXOrubicin: IV push/infusion over 1 - 15 minutes
Days 1, 8 and 15.
Dose: 25 mg/m^2/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein or central venous access device.

Pegaspargase: IV over 1 - 2 hours
Day 4
Dose: 2,500 International Units/m^2/dose
Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.

Special precautions:

1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Cyclophosphamide: IV over 30 - 60 minutes
Day 29
Dose: 1,000 mg/m^2/dose

Hydrate according to institutional guidelines. Suggested hydration: Pre-hydrate using fluids containing at least 0.45% NaCl. Achieve urine specific gravity of ≤ 1.010 prior to start of cyclophosphamide. Continue hydrating at a rate of 125 mL/m^2/hour IV/PO for at least 8 hours after cyclophosphamide administration.

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

Thioguanine: PO
Days 29 - 42.
Dose: 60 mg/m^2/dose/once daily*

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

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

Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details.

Cytarabine: IV over 1 - 30 minutes or subcutaneous
Days 29 - 32 and 36 - 39
Dose: 75 mg/m^2/dose/day

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

Methotrexate: Intrathecal (IT)
Days 1 and 29
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The Therapy Delivery Maps (TDMs) for Delayed Intensification are on the next two (2) pages.

For B-ALL and B-LLy patients: Following completion of Delayed Intensification, the next course (Interim Maintenance II, Section 4.6) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.5.1a Delayed Intensification (56 days)– AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C, and B-LLy Patients

_____ Patient name or initials _____ DOB

Delayed Intensification is 8 weeks (56 days). Begin DI on Day 57 of IM I or when ANC ≥ 750/µL and platelets ≥75,000/µL, whichever occurs later. See Section 4.5 for detailed therapy interruption guidelines.
This therapy delivery map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (may give IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID See Section 4.5 for administration guidelines	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[1] d. Bilirubin, ALT, & Creatinine e. Echocardiogram[2]
VinCRIStine (VCR)	IV push over 1 minute$^+$	1.5 mg/m^2/dose	Days 1, 8 & 15	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m^2/dose	Days 1, 8 & 15	See Section 4.5 for administration guidelines.	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Day 29*	See Section 4.5 for administration guidelines.	[1] Obtain with each IT administration [2] Prior to first dose of doxorubicin
Thioguanine (TG)	PO	60 mg/m^2/dose/day	Days 29*-42	See Section 4.5 & Appendix II for administration guidelines *for suggested dose based on TPMT and NUDT15 status, see Section 5.11	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose/day	Days 29-32 & 36-39		
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1 & 29	See Section 4.5 for administration guidelines **Note age-based dosing**	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	DEX ____mg ____mg	VCR ____mg	DOXO ____mg	PEG-ASP _____IU	CPM* ____mg	TG* _____mg	ARAC* _____mg	IT MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.									
		1	____mg ____mg	____mg	____mg					_____mg	a%, b, c, d, e#	
		2	↓									
		3										
		4				_____IU						
		5										
		6										
		7										
		8		____mg	____mg						a%, b	
		--										
		15	____mg ____mg	____mg	____mg						a%, b	
		16	↓									
		17										
		18										
		19										
		20										
		21										
		22										
			This Therapy Delivery Map continues on the next page									

***** Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy. # Prior to first doxorubicin dose

% **Note**: Height (Ht) is only required at the beginning of this course.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.5.1b **Delayed Intensification (56 days) – AR B-ALL Patients, LR Patients Randomized to Arm LR-C, and B-LLy Patients (Continued)**

_____ Patient name or initials _____ DOB

Delayed Intensification is 8 weeks (56 days). Begin DI on Day 57 of IM I or when ANC ≥ 750/µL and platelets ≥75,000/µL, whichever occurs later. See Section 4.5 for detailed therapy interruption guidelines. This therapy delivery map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (may give IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID See Section 4.5 for administration guidelines	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[1] d. Bilirubin, ALT, & Creatinine e. Echocardiogram[2] [1] Obtain with each IT administration [2] Prior to first dose of doxorubicin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m^2/dose	Days 1, 8 & 15	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m^2/dose	Days 1, 8 & 15	See Section 4.5 for administration guidelines.	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Day 29*	See Section 4.5 for administration guidelines	
Thioguanine (TG)	PO	60 mg/m^2/dose/day	Days 29*-42	See Section 4.5 & Appendix II for administration guidelines *for suggested dose based on TPMT and NUDT15 status, see Section 5.11	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose/day	Days 29-32 & 36-39		
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1 & 29	See Section 4.5 for administration guidelines **Note age-based dosing**	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	DEX ___mg ___mg	VCR ___mg	DOXO ___mg	PEG-ASP ___IU	CPM* ___mg	TG* ___mg	ARAC* ___mg	IT MTX ___mg	Studies	Comments (Include any held doses, or dose modifications)
		29*					___mg	___mg	___mg	___mg	a[%], b, c, d	
		30						↓	↓			
		31										
		32										

		36							___mg		b	
		37							↓			
		38										
		39										
		40										
		41										
		42						↓				
		43										
		--										
		50										

		56										
		57	**Begin next course (Interim Maintenance II, Section 4.6) on Day 57, or when blood count parameters are met (whichever occurs later)**									

***** Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy. [%] **Note**: Height (Ht) is only required at the beginning of this course.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.6 Interim Maintenance II (56 days) – AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C, and B-LLy Patients

NOTE FOR B-ALL PATIENTS: AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Criteria to Start Interim Maintenance II

Begin IM II on Day 57 of DI, or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later.

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

A) If ANC is < 500/µL or platelets < 50,000/µL, hold all chemotherapy and repeat blood counts in 4 days.
    1. In 4 days, if ANC ≥ 500/µL and platelets ≥ 50,000/µL, give same dose of methotrexate as previous cycle.
    2. In 4 days, if ANC is still < 500/µL or platelets < 50,000/µL, give VCR (and IT MTX if Day 31) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and IV MTX if counts are adequate.
        a. If after 7 days, ANC ≥ 500/µL and platelets ≥ 50,000/µL, reduce dose of MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A-C.
        b. If after 7 days ANC is still < 500/µL or platelets < 50,000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL. When ANC ≥ 500/µL and platelets ≥ 50,000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A-C.
B) If ANC ≥ 500/µL but < 750/µL and/or platelets ≥ 50,000/µL but < 75,000/µL, give same dose of MTX as previously (i.e. no escalation).
C) If ANC ≥ 750/µL and platelets ≥ 75,000/µL escalate MTX by 50 mg/m^2/dose.
D) Do not escalate MTX dose and resume at 80% of last dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume escalation as per A - C.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1, 11, 21, 31, and 41.
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Methotrexate: IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted).
Days 1, 11, 21, 31 and 41
Starting dose is two-thirds of the maximum tolerated dose attained in Interim Maintenance I. For example, if a patient has toxicity at 250 mg/m² on Interim Maintenance I, the starting dose for Interim Maintenance II will be two thirds of 200 mg/m^2 (or 130 mg/m^2) IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted). Subsequent doses will be escalated by 50 mg/m² every 10 days (± 2 days) for 4 doses, to toxicity Days 11, 21, 31 and 41.

Methotrexate: Intrathecal (IT)
Days 1 and 31
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

FOR PATIENTS WITH AR B-ALL: CONSENT TO 1 OF 4 DIFFERENT MAINTENANCE REGIMENS MUST TAKE PLACE BEFORE STARTING MAINTENANCE THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS RANDOMIZATION ARE OFF PROTOCOL THERAPY.

For patient convenience, consent for Maintenance therapy can be obtained any time from Day 41 of IM II to just prior to the planned start of Maintenance therapy and randomization via the RDE Callback form, can be done as early as 72 hours prior to and must be done before start of Maintenance therapy

LR B-ALL PATIENTS RANDOMIZED TO ARM LR-C WILL CONTINUE TO MAINTENANCE WHEN COUNT PARAMETERS ARE MET

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

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

For B-ALL Patients:
Following completion of Interim Maintenance II, the next course (Maintenance Arms A, B, C or D, Sections 4.7, 4.8, 4.9 or 4.10 - depending on randomization results for AR B-ALL patients; Maintenance Arm C, Section 4.9 for LR B-ALL patients on Arm LR-C) starts on Day 57 or when blood count parameters are met (whichever occurs later).

For B-LLy Patients:
Following completion of Interim Maintenance II, the next course (Maintenance Arm LLy, Section 4.11) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.6.1 **Interim Maintenance II – AR B-ALL Patients, LR B-ALL Patients Randomized to Arm LR-C and B-LLy Patients (56 days)**	_____ Patient name or initials _____ DOB

Interim Maintenance II begins on Day 57 of DI or when ANC ≥ 750/µL and platelets ≥ 75,000/µL whichever occurs later.
This course lasts 8 weeks (56 days) and this Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, & Creatinine. ! Obtain with each IT administration. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	IV over 2-5 min (undiluted) or 10-15 min (diluted)	____mg/m²/dose*	Days 1, 11, 21, 31 & 41	*Starting dose for Interim Maintenance II is two-thirds of the maximum tolerated dose attained in Interim Maintenance I (see Section 4.6 for details). Thereafter, **escalate by 50 mg/m²/dose** See Section 4.6 for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1 and 31	See Section 4.6 for administration guidelines **Note age-based dosing**	

Ht_____ cm Wt_____ kg BSA_____ m²

Date Due	Date Given	Day	VCR ____mg	IV MTX ____mg *(escalating dose)*	IT MTX ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual administered dose below.				
		1	____mg	____mg	____mg	a%, b, c, d	

		11	____mg	____mg		a%, b, d	

		21	____mg	____mg		a%, b, d	

		31	____mg	____mg	____mg	a%, b, c, d	

		41	____mg	____mg		a%, b, d	

		56					
		57	**Begin next course (Maintenance Arms A, B, C or D, Sections 4.7, 4.8, 4.9 or 4.10 - depending on randomization results for AR B-ALL patients; Maintenance Arm C, Section 4.9 for LR B-ALL patients on Arm LR-C); Maintenance Arm LLy, Section 4.11 for B-LLy patients on Day 57 or when blood count parameters are met (whichever occurs later).**				

% **Note**: Height (Ht) is only required at the beginning of this course.

DO CALL-BACK #2 PRIOR TO BEGINNING MAINTENANCE THERAPY FOR AR B-ALL PATIENTS

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.7 Maintenance Arm A (AR B-ALL Patients)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

CONSENT TO 1 OF 4 DIFFERENT MAINTENANCE REGIMENS MUST TAKE PLACE BEFORE STARTING MAINTENANCE THERAPY FOR PATIENTS WITH AR B-ALL. PATIENTS WHO ELECT NOT TO CONSENT TO THIS RANDOMIZATION ARE OFF PROTOCOL THERAPY.

For patient convenience, consent for Maintenance therapy can be obtained any time from Day 41 of IM II to just prior to the planned start of Maintenance therapy and randomization. Randomization via the RDE Callback form (Callback #2), must be done within 72 hours PRIOR TO the planned start of Maintenance therapy.

Treatment administered to AR B-ALL patients randomized to Maintenance treatment Arm A:

- Vincristine/dexamethasone pulses at **4 week** intervals,
- IT methotrexate every 12 weeks
- Oral methotrexate at **20 mg/m^2/week**.

Criteria to begin Maintenance

Maintenance begins on Day 57 of IM II, or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and dexamethasone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12 week cycles repeated until total duration of therapy is 2 years for female patients and 3 years for male patients from the start of Interim Maintenance I. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

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

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1, 29 & 57
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 5, 29 - 33 & 57 - 61(do not taper).
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)
Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**
Dose: **20 mg/m^2/dose** weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration.

Mercaptopurine: PO
Days 1 - 84
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.9 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

HRQOL Studies
Both HRQOL ancillary studies are closed to new patient enrollment due to accrual goals being met. Closure to accrual occurred on March 3, 2013 for the LPFS study and April 19, 2013 for the PLES study. Institutions are required to continue data collection at remaining evaluation time points, for patients already enrolled on these studies.

Please note: For AR B-ALL already patients enrolled on the optional Patient Leukemia Experience Study (available at all centers), evaluations are due on Day 29 (or within 1 month afterwards) of Cycles 1, 4, 7 and end of therapy for boys, Day 29 (or within 1 month afterwards) of Cycles 1, 4 and end of therapy for girls. See Section 15.0 for details of evaluation schedule.

For AR B-ALL patients already enrolled on the optional Leukemia Physical Functioning Study (at selected centers-available on the COG AALL0932 protocol webpage), evaluations for boys are due on Day 29 (or within 1 month afterwards) of Cycles 1, 7 and also 1 year post therapy; evaluations for girls are due on Day 29 (or within 1 month afterwards) of Cycle 1 and end of therapy, as well as 1 year post therapy. See Section 16.0 for details of evaluation schedule.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm A **(AR B-ALL patients)** is on the following page.

4.7.1 Maintenance - Treatment Arm A- Standard Treatment (AR B-ALL Patients)

_____ Patient name or initials

_____ DOB

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Sections 4.7 and 5.9 for details. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[1] d. Bilirubin, ALT, & Creatinine e. Patient Leukemia Experience Study surveys[2] f. Leukemia Physical Functioning Study evaluations[3] [1] Obtain with each IT administration [2] For the Patient Leukemia Experience study, boys' evaluations is due on Day 29 of Cycles 1, 4, 7 and also at end of therapy; for girls Cycles 1, 4 and also end of therapy. See Section 15.0 for details. [3]For the Physical Functioning study, evaluations for boys are due on Day 29 of Cycles 1, 7 & 1 year post therapy; evaluations for girls are due on Day 29 of Cycle 1, at the end of therapy and 1 year post therapy. See Section 16.0 for details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	Days 1-5, 29-33 & 57-61 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.7 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day*	Days 1-84	*see Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.7 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	**20 mg/m²/dose/week**	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	**Omit Day 1 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 1	See Section 4.7 for administration guidelines **Note age-based dosing**	

Enter Cycle #_____Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg	_____mg		a%, b, c, d	
		2							
		3							
		4							
		5							

		8					_____mg		

		15					_____mg		

-		22					_____mg		

		29	_____mg	_____mg _____mg			_____mg	a%, b, e, f	
		30							
		31							
		32							
		33							
		36					_____mg		

		43					_____mg		

		50					_____mg		

		57	_____mg	_____mg _____mg			_____mg	a%, b	
		58							
		59							
		60							
		61							

-		64					_____mg		

		71					_____mg		

		78					_____mg		

		84							
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs (females) or 3 yrs (males) from start of IM I**						

% **Note**: Height (Ht) is only required at the beginning of each course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.8 Maintenance Arm B (AR B-ALL Patients)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

CONSENT TO 1 OF 4 DIFFERENT MAINTENANCE REGIMENS MUST TAKE PLACE BEFORE STARTING MAINTENANCE THERAPY FOR PATIENTS WITH AR B-ALL. PATIENTS WHO ELECT NOT TO CONSENT TO THIS RANDOMIZATION ARE OFF PROTOCOL THERAPY.

For patient convenience, consent for Maintenance therapy can be obtained any time from Day 41 of IM II to just prior to the planned start of Maintenance therapy and randomization. Randomization via the RDE Callback form (Callback #2), must be done within 72 hours PRIOR TO the planned start of Maintenance therapy.

Treatment administered to AR B-ALL patients randomized to Maintenance treatment Arm B:

- Vincristine/dexamethasone pulses at **4 week** intervals,
- IT methotrexate every 12 weeks
- Oral methotrexate at **20 mg/m^2/week**.

Criteria to begin Maintenance

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/μL and platelets ≥ 75,000/μL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and dexamethasone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12 week cycles repeated until total duration of therapy is 2 years for female patients and 3 years for male patients from the start of Interim Maintenance I. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

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

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1, 29 & 57
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 5, 29 - 33 & 57 - 61 (do not taper).
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**
Dose: **20 mg/m^2/dose** weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration.
For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Effective the memo dated 01/13/2017 all patients on Arms B and D were recommended to have their oral methotrexate dose lowered to 20 mg/m^2/week, the standard of care therapy. Subsequently, patients should have their doses of 6 mercaptopurine and methotrexate adjusted based on tolerability following normal dose escalation procedures, as outlined in the protocol Section 5.9.

Mercaptopurine: PO
Days 1 - 84
Dose: 75 mg/m^2/dose daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.8 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1
Age-based dosing:

Age (yrs)	Dose

1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

HRQOL Studies

Both HRQOL ancillary studies are closed to new patient enrollment due to accrual goals being met. Closure to accrual occurred on March 3, 2013 for the LPFS study and April 19, 2013 for the PLES study. Institutions are required to continue data collection at remaining evaluation time points, for patients already enrolled on these studies.

Please note: For AR B-ALL patients already enrolled on the optional Patient Leukemia Experience Study (available at all centers), evaluations are due on Day 29 (or within 1 month afterwards) of Cycles 1, 4, 7 and end of therapy for boys; Day 29 (or within 1 month afterwards) of Cycles 1, 4 and end of therapy for girls. See Section 15.0 for details of evaluation schedule.

For AR B-ALL patients already enrolled on the optional Leukemia Physical Functioning Study (at selected centers available on the COG AALL0932 protocol webpage), evaluations for boys are due on Day 29 (or within 1 month afterwards) of Cycles 1, 7 and also 1 year post therapy; evaluations for girls are due on Day 29 (or within 1 month afterwards) of Cycle 1 and end of therapy, as well as 1 year post therapy. See Section 16.0 for details of evaluation schedule.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm B **(AR B-ALL patients)** is on the following page.

4.8.1 Maintenance - Treatment Arm B (AR B-ALL Patients)

Patient name or initials _____ DOB _____

Maintenance begins on day 57 of IM II or when peripheral counts recover to ANC ⩾ 750/µL and platelets ⩾ 75,000/µL, (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Sections 4.8 and 5.9 for details. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**	a. Hx, PE, Wt ., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[1] d. Bilirubin, ALT, & Creatinine e. Patient Leukemia Experience Study surveys[2] f. Leukemia Physical Functioning Study evaluations[3]
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	Days 1-5, 29-33 & 57-61 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.8 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day*	Days 1-84	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.8 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	**20 mg/m²/dose/week**	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	**Omit Day 1 dose as it coincides with IT MTX**	[1] Obtain with each IT administration [2] For the Patient Leukemia Experience study, boys' evaluations are due on Day 29 of Cycles 1, 4, 7 and also at end of therapy; for girls, Cycles 1, 4 and also end of therapy. See Section 15.0 for details. [3]For the Physical Functioning study; evaluations for boys are due on Day 29 of Cycles 1, 7 & 1 year post therapy; evaluations for girls are due on Day 29 of Cycle 1, at the end of therapy, and 1 year post therapy. See Section 16.0 for details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ⩾ 9 15 mg	Day 1	See Section 4.8 for administration guidelines **Note age-based dosing**	

Enter Cycle #_____ Ht _____ cm Wt _____ kg BSA _____ m²

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg	_____mg		a%, b, c, d	
		2							
		3							
		4							
		5							
		8					_____mg		
		15					_____mg		
		22					_____mg		
		29	_____mg	_____mg _____mg			_____mg	a%, b, e, f	
		30							
		31							
		32							
		33							
		36					_____mg		
		43					_____mg		
		50					_____mg		
		57	_____mg	_____mg _____mg			_____mg	a%, b	
		58							
		59							
		60							
		61							
		64					_____mg		
		71					_____mg		
		78					_____mg		
		84							
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs (females) or 3 yrs (males) from start of IM I**						

% **Note**: Height (Ht) is only required at the beginning of each course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.9 Maintenance Arm C (AR B-ALL Patients and LR B-ALL Patients Randomized to Arm LR-C)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

CONSENT TO 1 OF 4 DIFFERENT MAINTENANCE REGIMENS MUST TAKE PLACE BEFORE STARTING MAINTENANCE THERAPY FOR PATIENTS WITH AR B-ALL ONLY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS RANDOMIZATION ARE OFF PROTOCOL THERAPY.

For patient convenience, consent for Maintenance therapy can be obtained any time from Day 41 of IM II to just prior to the planned start of Maintenance therapy and randomization. Randomization via the RDE Callback form (Callback #2), must be done within 72 hours PRIOR TO the planned start of Maintenance therapy.

Treatment administered to AR B-ALL patients randomized to Maintenance treatment Arm C:

- Vincristine/dexamethasone pulses at **12 week** intervals,
- IT methotrexate every 12 weeks
- Oral methotrexate at **20 mg/m^2/week**.

Criteria to begin Maintenance

Maintenance begins on day 57 of IM II or when peripheral counts recover to ANC ≥ 750/μL and platelets ≥ 75,000/μL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and dexamethasone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12 week cycles repeated until total duration of therapy is 2 years for female patients and 3 years for male patients from the start of Interim Maintenance I. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

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

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 5 (do not taper).
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**
Dose: **20 mg/m^2/dose** weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 84
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.8 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

HRQOL Studies
Both HRQOL ancillary studies are closed to new patient enrollment due to accrual goals being met. Closure to accrual occurred on March 3, 2013 for the LPFS study and April 19, 2013 for the PLES study. Institutions are required to continue data collection at remaining evaluation time points, for patients already enrolled on these studies.

Please note: For AR B-ALL patients already enrolled on the optional Patient Leukemia Experience Study, evaluations are due on Day 29 (or within 1 month afterwards) of Cycles 1, 4, 7 and end of therapy for boys; Day 29 (or within 1 month afterwards) of Cycles 1, 4 and end of therapy for girls. See Section 15.0 for details of evaluation schedule.

For AR B-ALL patients already enrolled on the optional Leukemia Physical Functioning Study, evaluations for boys are due on Day 29 (or within 1 month afterwards) of Cycles 1, 7 and also 1 year post therapy; evaluations for girls are due on Day 29 (or within 1 month afterwards) of Cycle 1 and end of therapy, as well as 1 year post therapy. See Section 16.0 for details of evaluation schedule.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm C **(AR B-ALL patients and LR B-ALL Patients Randomized to Arm LR-C)** is on the following page.

4.9.1 Maintenance - Treatment Arm C (AR B-ALL Patients and LR B-ALL Patients Randomized to Arm LR-C)

Patient name or initials _____ DOB _____

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL, (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Sections 4.9 and 5.9 for details. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Day 1	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[1] d. Bilirubin, ALT, & Creatinine e. Patient Leukemia Experience Study surveys[2] f. Leukemia Physical Functioning Study evaluation[3]. [1] Obtain with each IT administration [2] For the Patient Leukemia Experience study, boys' evaluations are due on Day 29 of Cycles 1, 4, 7 and also at end of therapy; for girls Cycles 1, 4 and also end of therapy. See Section 15.0. [3]For the Physical Functioning study; evaluations for boys are due on Day 29 of Cycles 1, 7 & 1 year post therapy; evaluations for girls are due on Day 29 of Cycle 1, at the end of therapy and 1 year post therapy. See Section 16.0 for details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	Days 1-5 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.9 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day*	Days 1-84	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.9 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	**20 mg/m²/dose/week**	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	**Omit Day 1 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 1	See Section 4.9 for administration guidelines **Note age-based dosing**	

Enter Cycle #_____ Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg	_____mg		a%, b, c, d	
		2							
		3							
		4							
		5							

		8					_____mg		

		15					_____mg		

		22					_____mg		

		29					_____mg	a%, b, e, f	

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57					_____mg	a%, b	

		64					_____mg		

		71					_____mg		

		78					_____mg		

		84							
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs (females) or 3 yrs (males) from start of IM I**						

% **Note**: Height (Ht) is only required at the beginning of each course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.10 Maintenance Arm D (AR B-ALL Patients)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST-INDUCTION THERAPY ON THIS PROTOCOL.

CONSENT TO 1 OF 4 DIFFERENT MAINTENANCE REGIMENS MUST TAKE PLACE BEFORE STARTING MAINTENANCE THERAPY FOR PATIENTS WITH AR B-ALL. PATIENTS WHO ELECT NOT TO CONSENT TO THIS RANDOMIZATION ARE OFF PROTOCOL THERAPY.

For patient convenience, consent for Maintenance therapy can be obtained any time from Day 41 of IM II to just prior to the planned start of Maintenance therapy and randomization. Randomization via the RDE Callback form (Callback #2), must be done within 72 hours PRIOR TO the planned start of Maintenance therapy.

Treatment administered to AR B-ALL patients randomized to Maintenance treatment Arm D:

- Vincristine/dexamethasone pulses at **12 week** intervals,
- IT methotrexate every 12 weeks
- Oral methotrexate at **20 mg/m^2/week**.

Criteria to begin Maintenance

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/μL and platelets ≥ 75,000/μL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and dexamethasone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12 week cycles repeated until total duration of therapy is 2 years for female patients and 3 years for male patients from the start of Interim Maintenance I. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

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

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 5(do not taper).
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**
Dose: **20 mg/m^2/dose** weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Effective the memo dated 01/13/2017 all patients on Arms B and D were recommended to have their oral methotrexate dose lowered to 20 mg/m^2/week, the standard of care therapy. Subsequently, patients should have their doses of 6 mercaptopurine and methotrexate adjusted based on tolerability following normal dose escalation procedures, as outlined in the protocol Section 5.9.

Mercaptopurine: PO
Days 1 - 84
Dose: 75 mg/m^2/dose daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.8 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1
Age-based dosing:
Age (yrs) Dose

1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

HRQOL Studies
Both HRQOL ancillary studies are closed to new patient enrollment due to accrual goals being met. Closure to accrual occurred on March 3, 2013 for the LPFS study and April 19, 2013 for the PLES study. Institutions are required to continue data collection at remaining evaluation time points, for patients already enrolled on these studies.

Please note: For AR B-ALL patients already enrolled on the optional Patient Leukemia Experience Study, evaluations are due on Day 29 (or within 1 month afterwards) of Cycles 1, 4, 7 and end of therapy for boys; Day 29 (or within 1 month afterwards) of Cycles 1, 4 and end of therapy for girls. See Section 15.0 for details of evaluation schedule.

For AR B-ALL patients already enrolled on the optional Leukemia Physical Functioning Study, evaluations for boys are due on Day 29 (or within 1 month afterwards) of Cycles 1, 7 and also 1 year post therapy; evaluations for girls are due on Day 29 (or within 1 month afterwards) of Cycle 1 and end of therapy, as well as 1 year post therapy. See Section 16.0 for details of evaluation schedule.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm D **(AR B-ALL patients)** is on the following page.

4.10.1 Maintenance - Treatment Arm D (AR B-ALL Patients)

Patient name or initials _____ DOB _____

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL, (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Sections 4.10 and 5.9 for details This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Day 1	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	Days 1-5 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.10 for administration guidelines
Mercaptopurine (MP)	PO	75 mg/m²/dose/day*	Days 1-84	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.10 & Appendix I for administration guidelines
Methotrexate (MTX)	PO	**20 mg/m²/dose/week**	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	Omit Day 1 dose as it coincides with IT MTX
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 1	See Section 4.10 for administration guidelines **Note age-based dosing**

OBSERVATIONS

a. Hx, PE, Wt., Ht.
b. CBC/diff/platelets
c. CSF cell count, cytospin[1]
d. Bilirubin, ALT, & Creatinine
e. Patient Leukemia Experience Study surveys[2]
f. Leukemia Physical Functioning Study evaluation[3]

[1] Obtain with each IT administration

[2] For the Patient Leukemia Experience study, boys' evaluations are due on Day 29 of Cycles 1, 4, 7 and also at end of therapy; for girls Cycles 1, 4 and also end of therapy. See Section 15.0

[3]For the Physical Functioning study; evaluations for boys are due on Day 29 of Cycles 1, 7 & 1 year post therapy; evaluations for girls are due on Day 29 of Cycle 1, at the end of therapy and 1 year post therapy. See Section 16.0 for details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Enter Cycle # _____ Ht_____cm Wt_____ kg BSA_____m²

Date Due	Date Given	Day	VCR ____mg	DEX ____mg ____mg	MP ____mg	IT MTX ____mg	PO MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below.						
		1	____mg	____mg ____mg	____mg	____mg		a%, b, c, d	
		2							
		3							
		4							
		5							

		8					____mg		

		15					____mg		

		22					____mg		

		29					____mg	a%, b, e, f	

		36					____mg		

		43					____mg		

		50					____mg		

		57					____mg	a%, b	

		64					____mg		

		71					____mg		

		78					____mg		

		84							
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs (females) or 3 yrs (males) from start of IM I**						

% **Note**: Height (Ht) is only required at the beginning of each course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.11 Maintenance Arm LLy (B-LLy Patients)

PATIENTS ARE NON-RANDOMLY ASSIGNED TO CONTINUE MAINTENANCE ARM LLy THERAPY. CALLBACK #2 IS NOT SUBMITTED FOR B-LLy PATIENTS.

Criteria to begin Maintenance
Maintenance begins on Day 57 of IM II, or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and dexamethasone will be delivered as scheduled, despite myelosuppression.

B-LLy patients will be non-randomly assigned to Maintenance Arm LLy:
- Vincristine/dexamethasone pulses at **4 week** intervals,
- IT methotrexate every 12 weeks
- Oral methotrexate at **20 mg/m^2/week**.

Maintenance consists of 12 week cycles repeated until total duration of therapy is 2 years from the start of Interim Maintenance I for both male and female patients. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

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

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for
special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1, 29 & 57
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 5, 29 - 33 & 57 - 61(do not taper).
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**
Dose: **20 mg/m^2/dose** weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration.

Mercaptopurine: PO
Days 1 - 84
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.9 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm LLy **(B-LLy patients)** is on the following page.

4.11.1 Maintenance Arm LLy (B-LLy Patients only)

_____ Patient name or initials _____ DOB

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL whichever occurs later for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Sections 4.11 and 5.9 for details. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**	a Hx, PE, Wt., Ht. b CBC/diff/platelets c CSF cell count, cytospin! d Bilirubin, ALT, & Creatinine e. CT (neck, chest, abdomen & pelvis), CXR, bone scan (if bone involvement) ^ !Obtain with each IT administration ^Please refer to Section 7.1d for details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	Days 1-5, 29-33 & 57-61 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.11 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day*	Days 1-84	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.11 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	**20 mg/m²/dose/week**	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	**Omit Day 1 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 1	See Section 4.11 for administration guidelines **Note age-based dosing**	

Enter Cycle # _____ Ht _____ cm Wt _____ kg BSA _____ m²

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg	_____mg		a%, b, c, d	
		2							
		3							
		4							
		5							

		8					_____mg		

		15					_____mg		

-		22					_____mg		

		29	_____mg	_____mg _____mg			_____mg	a%, b	
		30							
		31							
		32							
		33							

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57	_____mg	_____mg _____mg			_____mg	a%, b	
		58							
		59							
		60							
		61							

-		64					_____mg		

		71					_____mg		

		78					_____mg		

		84						e^	
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs from start of IM I for both males and females.**						

% **Note**: Height (Ht) is only required at the beginning of each course/cycle.

^At completion of Maintenance therapy. **Note**: CXR is not required if CT chest is done (see Section 7.1d for details).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.12 Consolidation (19 Weeks) – LR B-ALL Patients Randomized to Arm LR-M

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

PATIENTS DETERMINED TO BE LOW RISK MUST CONSENT TO BE RANDOMIZED FOR POST-INDUCTION THERAPY BEFORE STARTING CONSOLIDATION. PATIENTS WHO ELECT NOT TO CONSENT TO THIS TREATMENT RANDOMIZATION ARE OFF PROTOCOL THERAPY.

Day 1 of Consolidation begins one week after the end of Induction regardless of counts.

However, oral 6-MP should not be started until ANC ≥ 500/µL and platelets ≥ 75,000/µL.

If the start of oral 6-MP is delayed, DO NOT "make up" missed doses. It is recommended to repeat a CBC every 2 to 3 days and start oral 6-MP when counts meet criteria; deliver initial IV MTX 2 weeks after end of Induction (i.e. on Day 8 of Consolidation) if count parameters are met regardless of the length of 6-MP administration. If count parameters are not met, patient will begin Day 8 of Consolidation as soon as they are met.

Each MTX infusion is to begin when ANC ≥ 500/µL and platelets ≥ 75,000/µL; ALT < 20 x upper limit of normal and bilirubin and creatinine normal for age.

After an IV dose of MTX is given, continue with oral 6-MP for the next 3 weeks even in the face of uncomplicated myelosuppression.

When a course of IV MTX is due and ANC < 500/µL and/or platelets < 75,000/µL, delay IV MTX administration and HOLD 6-MP until ANC ≥ 500/µL and platelets ≥ 75,000/µL, then restart 6-MP and IV MTX at 100% dosing. IV MTX should continue on an every 3-week schedule.

When a subsequent course of IV MTX is due and ANC < 500/µL and/or platelets < 75,000/µL, delay IV MTX administration and HOLD 6-MP until count recovery and then restart 6-MP at 75% dose and IV MTX at 100% dosing. IV MTX should continue on an every 3 week schedule.

See Section 5.7.2 for additional details of dose modification for this course.

Also consider TMP/SMX as possible cause of neutropenia. Consider discontinuing TMP/SMX in favor of an alternative approach to Pneumocystis prophylaxis, as per COG Supportive Care Guidelines (see https://members.childrensoncologygroup.org/prot/reference_materials.asp.

For patients with TPMT and NUDT15 mutations see Section 5.9 for starting doses of 6-MP.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 15, 22, 78 and 85
Dose: 1.5 mg/m^2/dose (maximum 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Methotrexate: IV over 24 hours
Days 8, 29, 50, 71, 92 and 113
Dose: 1000 mg/m^2

Given as a 200 mg/m^2 bolus over 20 - 30 minutes followed by 800 mg/m^2 over 23.5 hours (if initial bolus was over 30 minutes) or 23 hours and 40 minutes (if initial bolus was over 20 minutes).

The goal is to complete the intermediate dose methotrexate infusion in 24 hours; however, due to infusion pump variability, acceptable total infusion time is 24 ± 2 hours.

Leucovorin rescue begins at 10 mg/m^2 every 6 hours beginning 42 hrs after the start of the infusion. Continue leucovorin until plasma MTX is < 0.2µM. If the patient has had clinical toxicity (see definition below) on a prior cycle, consider giving the 54 hour dose of leucovorin even if the 48 hour MTX is < 0.2 µM. Methotrexate levels are drawn at the end of methotrexate infusion and 24 hours after completion of the methotrexate infusion and every 12 to 24 hours thereafter until the level is < 0.2 µM. See Section 5.7.2 for more detailed recommendations on hydration and leucovorin administration.

Suggested hydration and alkalinization:
Pre-hydrate with D_5 ¼ NS with 30 mEq/L sodium bicarbonate at 100 mL/m^2/hour until urine specific gravity is ≤ 1.010 and urine pH is ≥ 6.5 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 minutes) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration. Continue with hydration until plasma MTX level is < 0.2µM.

Special precautions**:** IV leucovorin and sodium bicarbonate are incompatible

See Section 5.7.2 for Toxicity Monitoring

Leucovorin: PO (may be given IV if necessary)
Days 9 - 10, 30 - 31, 51 - 52, 72 - 73, 93 - 94, and 114 - 115
Dose: 10 mg/m^2/dose for at least 2 doses given 42 and 48 hours after the **START** of MTX infusion, and continuing q 6 hours until MTX plasma MTX level is < 0.2µM

Leucovorin rescue will be given after IV MTX during Consolidation therapy. The first dose beginning 42 hrs after the **START** of the methotrexate infusion. Continue leucovorin until plasma methotrexate is < 0.2µM. In the absence of toxicity, the Hour 54 leucovorin dose should be eliminated if the 48 Hour plasma methotrexate concentration is < 0.2 µM. In case of prolonged clearance see Section 5.7.2

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

Methotrexate: Intrathecal (IT)*
Days 8, 29, 50, 71, 92 and 113
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

*Deliver IT therapy within 6 hrs of the beginning of the IV methotrexate infusion. (Hour -6 to +6, with hour 0 being the start of the MTX bolus)

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Dexamethasone: PO (may be given IV)
Days 15 - 21 and 78 - 84
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/day, divided BID) may be used temporarily as needed.

Mercaptopurine: PO
Days 1 - 133
Dose: 50 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 350 mg/m^2/week as possible. See Appendix III for details. Do not escalate dose based on blood counts during this cycle (see Section 5.8).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

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

Following completion of Consolidation, the next course (Maintenance Arm LR-M - Cycle 1, Section 4.13) starts on Day 134 or when blood count parameters are met (whichever occurs later).

4.12.1a **Consolidation (19 weeks) – LR B-ALL Patients Randomized to Arm LR-M**

Leucovorin rescue will be given after each IV MTX

_____ Patient name or initials _____ DOB

Consolidation therapy lasts 19 weeks. Start Consolidation on Day 36 of Induction (1 week after the end of Induction) regardless of counts but oral 6-MP should not be started until ANC ≥ 500/µL and platelets ≥75,000/µL. This Therapy Delivery Map is on **three (3)** pages. See Section 4.12 .for full treatment details.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Mercaptopurine (MP)	PO	50 mg/m^2/dose*	Days 1-133	See Section 4.12 & Appendix III for administration guidelines. *For TMPT and NUDT15 based dosing see Section 5.9	a. Hx/PE/Wt., Ht. b. CBC/Diff/Platelets c. CSF cell count, cytospin [1] d. Bilirubin , ALT, & Creatinine e. Serum creatinine & plasma MTX levels [2] [1] Obtain with each IT administration [2] See Section 7.1b for details of monitoring. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m^2/dose	Days 15, 22, 78, and 85	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX)	PO (may give IV)	3 mg/m^2/dose BID	Days 15-21 and 78-84	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.12 for admin guidelines	
Methotrexate (MTX)	IV over 24 hours	1000 mg/m^2	Days 8, 29, 50, 71, 92, and 113	See Section 4.12 for administration guidelines	
Leucovorin (LCV)	PO[#]	10 mg/m^2/dose q6 hrs	Days 9-10, 30-31, 51-52, 72-73, 93-94, and 114-115	See Section 4.12 for administration guidelines 42, 48 hrs after the **START** of each IV MTX and q6 hours until the MTX level falls below 0.2µM. [#]Continue until MTX level is < 0.2µM.	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 8, 29, 50, 71, 92, and 113	See Section 4.12 for administration guidelines. Deliver IT therapy within 6 hrs of the beginning of the IV methotrexate infusion. (Hour -6 to +6, with hour 0 being the start of the MTX bolus) **Note age-based dosing**	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	MP ____mg	VCR ____mg	DEX (BID Dosing) ____mg ____mg	IV MTX ____mg	IT MTX ____mg	LCV ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below							
		1	____mg						a[%], b	

		8				____mg	____mg		a[%], b, c, d	
		9						____mg	e	
		10						____mg	e	

		15		____mg	____mg ____mg				a[%]	
		16			____mg ____mg					
		17			____mg ____mg					
		18			____mg ____mg					
		19			____mg ____mg					
		20			____mg ____mg					
		21			____mg ____mg					
		22		____mg					a	

		29				____mg	____mg		a[%], b, c, d	
		30						____mg	e	
		31						____mg	e	

			This Therapy Delivery Map continues on the next two (2) pages.							

[%] **Note**: Height (Ht) is only required at the beginning of this course.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.12.1b Consolidation (19 weeks) – LR B-ALL Patients Randomized to Arm LR-M (Continued)

Leucovorin rescue will be given after each IV MTX

_____ Patient name or initials

_____ DOB

Consolidation therapy lasts 19 weeks. Start Consolidation on Day 36 of Induction (1 week after the end of Induction) regardless of counts but oral 6-MP should not be started until ANC ≥ 500/µL and platelets ≥ 75,000/µL. This Therapy Delivery Map is on three (3) pages. See Section 4.12 for full treatment details.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Mercaptopurine (MP)	PO	50 mg/m^2/dose*	Days 1-133	See Section 4.12 & Appendix III for administration guidelines. *For TMPT and NUDT15 based dosing see Section 5.9	a. Hx/PE/Wt., Ht. b. CBC/Diff/Platelets c. CSF cell count, cytospin [1] d. Bilirubin, ALT, & Creatinine e. Serum creatinine & plasma MTX levels [2] [1] Obtain with each IT administration [2] See Section 7.1b for details of monitoring. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 15, 22, 78, and 85	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX)	PO (may give IV)	3 mg/m^2/dose BID	Days 15-21 and 78-84	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.12 for admin guidelines	
Methotrexate (MTX)	IV over 24 hours	1000 mg/m^2	Days 8, 29, 50, 71, 92, and 113	See Section 4.12 for administration guidelines	
Leucovorin (LCV)	PO#	10 mg/m^2/dose q6 hrs	Days 9-10, 30-31, 51-52, 72-73, 93-94, and 114-115	See Section 4.12 for administration guidelines 42, 48 hrs after the **START** of each IV MTX and q6 hours until the MTX level falls below 0.2µM. #Continue until MTX level is < 0.2µM.	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 8, 29, 50, 71, 92, and 113	See Section 4.12 for administration guidelines. Deliver IT therapy within 6 hrs of the beginning of the IV methotrexate infusion. (Hour -6 to +6, with hour 0 being the start of the MTX bolus) **Note age-based dosing**	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	MP ____mg	VCR ____mg	DEX (BID Dosing) ____mg ____mg	IV MTX ____mg	IT MTX ____mg	LCV ____mg	Studies	Comments (Include any held doses, or dose modifications)
		43	____mg							

		50				____mg	____mg		a%, b, c, d	
		51						____mg	e	
		52						____mg	e	

		71				____mg	____mg		a%, b, c, d	
		72						____mg	e	
		73						____mg	e	

		78		____mg	____mg ____mg				a%	
		79			____mg ____mg					
		80			____mg ____mg					
		81			____mg ____mg					
		82			____mg ____mg					
		83			____mg ____mg					
		84			____mg ____mg					
		85		____mg					a%	

		This Therapy Delivery Map continues on the next page.								

% **Note**: Height (Ht) is only required at the beginning of this course.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.12.1c **Consolidation (19 weeks) – LR B-ALL Patients Randomized to Arm LR-M (Continued)**

Leucovorin rescue will be given after each IV MTX

_____ Patient name or initials _____ DOB

Consolidation therapy lasts 19 weeks. Start Consolidation on Day 36 of Induction (1 week after the end of Induction) regardless of counts but oral 6-MP should not be started until ANC > 500/µL and platelets > 75,000/µL. This Therapy Delivery Map is on three (3) pages. See Section 4.12 for full treatment details.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Mercaptopurine (MP)	PO	50 mg/m^2/dose*	Days 1-133	See Section 4.12 & Appendix III for administration guidelines. *For TMPT and NUDT15 based dosing see Section 5.9	a. Hx/PE/Wt., Ht. b. CBC/Diff/Platelets c. CSF cell count, cytospin [1] d. Bilirubin, ALT, & Creatinine e. Serum creatinine & plasma MTX levels [2] [1] Obtain with each IT administration [2] See Section 7.1b for details of monitoring. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute$^+$	1.5 mg/m^2/dose	Days 15, 22, 78, and 85	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX)	PO (may give IV)	3 mg/m^2/dose BID	Days 15-21 and 78-84	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.12 for admin guidelines	
Methotrexate (MTX)	IV over 24 hours	1000 mg/m^2	Days 8, 29, 50, 71, 92, and 113	See Section 4.12 for administration guidelines	
Leucovorin (LCV)	PO[#]	10 mg/m^2/dose q6 hrs	Days 9-10, 30-31, 51-52, 72-73, 93-94, and 114-115	See Section 4.12 for administration guidelines 42, 48 hrs after the **START** of each IV MTX and q6 hours until the MTX level falls below 0.2µM. [#]Continue until MTX level is < 0.2µM.	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 8, 29, 50, 71, 92, and 113	See Section 4.12 for administration guidelines. Deliver IT therapy within 6 hrs of the beginning of the IV methotrexate infusion. (Hour -6 to +6, with hour 0 being the start of the MTX bolus) **Note age-based dosing**	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	MP ____mg	VCR ____mg	DEX (BID Dosing) ____mg ____mg	IV MTX ____mg	IT MTX ____mg	LCV ____mg	Studies	Comments (Include any held doses, or dose modifications)
		92	____mg			____mg	____mg		a[%], b, c, d	
		93						_____mg	e	
		94						_____mg	e	

		99								

		106								

		113				____mg	____mg		a[%], b, c, d	
		114						_____mg	e	
		115						_____mg	e	

		120								

		127								

		133								
		134	**Start next course (Maintenance Arm LR-M – Cycle 1, Section 4.13) on Day 134 or when blood count parameters are met (whichever occurs later)**							

[%] **Note**: Height (Ht) is only required at the beginning of this course.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.13 Maintenance Arm LR-M – Cycle 1 (LR B-ALL Patients Randomized to Arm LR-M)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Criteria to begin Maintenance
Begin Maintenance therapy on Day 134 of Consolidation or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets. Only oral Mercaptopurine and Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. IT MTX, VCR and DEX will be delivered as scheduled despite myelosuppression.

The administration schedule below describes one 16 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 7 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID) x 7 days

Dose is adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 92, 99, and 106. **Omit Day 1 and Day 85 dose as it coincides with IT MTX**

Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 112
Dose: 75 mg/m^2 once daily* **(Note Higher 6-MP Dose than in Consolidation)**

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details.

Methotrexate: Intrathecal (IT)
Days 1 and 85
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Maintenance consists of cycles every 16 weeks until a total duration of therapy of 2½ years from the date of diagnosis is reached for both boys and girls. Therapy may be stopped on that date if the 7 day dexamethasone is completed for the cycle (i.e. complete all 7 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm LR-M Cycle 1 is on the following page.

Following completion of Maintenance Arm LR-M Cycle 1, the next course (Maintenance Arm LR-M Cycle 2, Section 4.14) starts on Day 113.

4.13.1 Maintenance Arm LR-M (Cycle 1) – LR B-ALL Patients Randomized to Arm LR-M

_____ Patient name or initials

_____ DOB

Maintenance Cycle 1 lasts 16 weeks. Therapy begins on Day 134 of Consolidation or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL, (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Sections 4.13 and 5.9 for details. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1 and 8	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, Creatinine, ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	Days 1-7 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.13 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day*	Days 1-112	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.13 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m²/dose/week	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 92, 99, and 106	**Omit Day 1 and 85 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 1 and 85	See Section 4.13 for administration guidelines **Note age-based dosing**	

Ht_____cm Wt_____ kg BSA_____m²

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg	_____mg		a%, b, c, d	
		2							
		3							
		4							
		5							
		6							
		7							
		8	_____mg				_____mg		

		15					_____mg		

		22					_____mg		

		29					_____mg	a%, b	

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57					_____mg	a%, b	

		64					_____mg		

		71					_____mg		

		78					_____mg		

		85				_____mg		a%, b, c	

		92					_____mg		

		99					_____mg		

		106					_____mg		

		112							
		113	**Begin Cycle 2 (Section 4.14). Repeat cycles based on dose modifications for low counts or low platelets until 2½ yrs from diagnosis for both boys and girls.**						

% **Note**: Height (Ht) is only required at the beginning of this course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.14 Maintenance Arm LR-M – Cycle 2 (LR B-ALL Patients Randomized to Arm LR-M)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Please follow the dose modifications for low ANC or low platelets. Only oral Mercaptopurine and Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. IT MTX, VCR and DEX will be delivered as scheduled despite myelosuppression.

The administration schedule below describes one 16 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 7 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID) x 7 days

Dose is adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 1, 8, 15, 22, 29, 36, 43, 50, 64, 71, 78, 85, 92, 99, and 106. **Omit Day 57 dose as it coincides with IT MTX**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 112
Dose: 75 mg/m^2 once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details.

Methotrexate: Intrathecal (IT)
Day 57
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Maintenance consists of cycles every 16 weeks until a total duration of therapy of 2½ years from the date of diagnosis is reached for both boys and girls. Therapy may be stopped on that date if the 7 day dexamethasone is completed for the cycle (i.e. complete all 7 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm LR-M Cycle 2 is on the following page.

Following completion of Maintenance Arm LR-M Cycle 2, the next course (Maintenance Arm LR-M Cycle 3, Section 4.15) starts on Day 113.

4.14.1 Maintenance Arm LR-M (Cycle 2) – LR B-ALL Patients Randomized to Arm LR-M

Patient name or initials _____ DOB _____

Maintenance Cycle 2 lasts 16 weeks. Therapy begins on Day 113 of Maintenance Cycle 1. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1 and 8	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, Creatinine, ! Obtain with each IT administration
Dexamethasone (DEX)	PO	3 mg/m^2/dose BID	Days 1-7 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.14 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m^2/dose/day*	Days 1-112	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.14 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m^2/dose/week	Days 1, 8, 15, 22, 29, 36, 43, 50, 64, 71, 78, 85, 92, 99, and 106	**Omit Day 57 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 57	See Section 4.14 for administration guidelines **Note age-based dosing**	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

_____Ht_____cm **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg		_____mg	a%, b, d	
		2							
		3							
		4							
		5							
		6							
		7							
		8	_____mg				_____mg		

		15					_____mg		

		22					_____mg		

		29					_____mg	a%, b	

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57				_____mg		a%, b, c	

		64					_____mg		

		71					_____mg		

		78					_____mg		

		85					_____mg	a%, b	

		92					_____mg		

		99					_____mg		

		106					_____mg		

		112							
		113	**Begin Cycle 3 (Section 4.15). Repeat cycles based on dose modifications for low counts or low platelets until 2½ yrs from diagnosis for both boys and girls.**						

% **Note**: Height (Ht) is only required at the beginning of this course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.15 Maintenance Arm LR-M – Cycle 3 (LR B-ALL Patients Randomized to Arm LR-M)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Please follow the dose modifications for low ANC or low platelets. Only oral Mercaptopurine and Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. IT MTX, VCR and DEX will be delivered as scheduled despite myelosuppression.

The administration schedule below describes one 16 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 7 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID) x 7 days

Dose is adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 1, 8, 15, 22, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, and 106. **Omit Day 29 dose as it coincides with IT MTX**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 112
Dose: 75 mg/m^2 once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details.

Methotrexate: Intrathecal (IT)
Day 29
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Maintenance consists of cycles every 16 weeks until a total duration of therapy of 2½ years from the date of diagnosis is reached for both boys and girls. Therapy may be stopped on that date if the 7 day dexamethasone is completed for the cycle (i.e. complete all 7 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm LR-M Cycle 3 is on the following page.

Following completion of Maintenance Arm LR-M Cycle 3, the next course (Maintenance Arm LR-M Cycle 4, Section 4.16) starts on Day 113.

4.15.1 Maintenance Arm LR-M (Cycle 3) – LR B-ALL Patients Randomized to Arm LR-M

_____ Patient name or initials

_____ DOB

Maintenance Cycle 3 lasts 16 weeks. Therapy begins on Day 113 of Maintenance Cycle 2. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1 and 8	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, Creatinine ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m^2/dose BID	Days 1-7 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.15 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m^2/dose/day*	Days 1-112	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.15 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m^2/dose/week	Days 1, 8, 15, 22, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, and 106	**Omit Day 29 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 29	See Section 4.15 for administration guidelines **Note age-based dosing**	

_____Ht_____cm **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg		_____mg	a%, b, d	
		2							
		3							
		4							
		5							
		6							
		7							
		8	_____mg				_____mg		

		15					_____mg		

		22					_____mg		

		29				_____mg		a%, b, c	

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57					_____mg	a%, b	

		64					_____mg		

		71					_____mg		

		78					_____mg		

		85					_____mg	a%, b	

		92					_____mg		

		99					_____mg		

		106					_____mg		

		112							
		113	**Begin Cycle 4 (Section 4.16). Repeat cycles based on dose modifications for low counts or low platelets until 2½ yrs from diagnosis for both boys and girls.**						

% **Note**: Height (Ht) is only required at the beginning of this course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.16 Maintenance Arm LR-M – Cycle 4 (LR B-ALL Patients Randomized to Arm LR-M)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Please follow the dose modifications for low ANC or low platelets. Only oral Mercaptopurine and Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. IT MTX, VCR and DEX will be delivered as scheduled despite myelosuppression.

The administration schedule below describes one 16 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 7 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID) x 7 days

Dose is adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 92, 99, and 106. **Omit Day 1 and 85 dose as it coincides with IT MTX**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 112
Dose: 75 mg/m^2 once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details.

Methotrexate: Intrathecal (IT)
Day 1 and 85
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Maintenance consists of cycles every 16 weeks until a total duration of therapy of 2½ years from the date of diagnosis is reached for both boys and girls. Therapy may be stopped on that date if the 7 day dexamethasone is completed for the cycle (i.e. complete all 7 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm LR-M Cycle 4 is on the following page.

Following completion of Maintenance Arm LR-M Cycle 4, the next course (Maintenance Arm LR-M Cycle 5, Section 4.17) starts on Day 113.

4.16.1 Maintenance Arm LR-M (Cycle 4) – LR B-ALL Patients Randomized to Arm LR-M

_____ Patient name or initials

_____ DOB

Maintenance Cycle 4 lasts 16 weeks. Therapy begins on Day 113 of Maintenance Cycle 3. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1 and 8	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, Creatinine ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m^2/dose BID	Days 1-7 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.16 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m^2/dose/day*	Days 1-112	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.16 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m^2/dose/week	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 92, 99, and 106	**Omit Day 1 and 85 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 1 and 85	See Section 4.16 for administration guidelines **Note age-based dosing**	

_____Ht_____cm **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg	_____mg		a%, b, c, d	
		2							
		3							
		4							
		5							
		6							
		7							
		8	_____mg				_____mg		

		15					_____mg		

		22					_____mg		

		29					_____mg	a%, b	

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57					_____mg	a%, b	

		64					_____mg		

		71					_____mg		

		78					_____mg		

		85				_____mg		a%, b, c	

		92					_____mg		

		99					_____mg		

		106					_____mg		

		112							
		113	**Begin Cycle 5 (Section 4.17). Repeat cycles based on dose modifications for low counts or low platelets until 2½ yrs from diagnosis for both boys and girls.**						

% **Note**: Height (Ht) is only required at the beginning of this course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.17 Maintenance Arm LR-M – Cycle 5 (LR B-ALL Patients Randomized to Arm LR-M)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Please follow the dose modifications for low ANC or low platelets. Only oral Mercaptopurine and Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. IT MTX, VCR and DEX will be delivered as scheduled despite myelosuppression.

The administration schedule below describes one 16 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 7 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID) x 7 days

Dose is adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 1, 8, 15, 22, 29, 36, 43, 50, 64, 71, 78, 85, 92, 99, and 106. **Omit Day 57 dose as it coincides with IT MTX**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 112
Dose: 75 mg/m^2 once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details.

Methotrexate: Intrathecal (IT)
Day 57
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Maintenance consists of cycles every 16 weeks until a total duration of therapy of 2½ years from the date of diagnosis is reached for both boys and girls. Therapy may be stopped on that date if the 7 day dexamethasone is completed for the cycle (i.e. complete all 7 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm LR-M Cycle 5 is on the following page.

Following completion of Maintenance Arm LR-M Cycle 5, the next course (Maintenance Arm LR-M Cycle 6, Section 4.18) starts on Day 113.

4.17.1 Maintenance Arm LR-M (Cycle 5) – LR B-ALL Patients Randomized to Arm LR-M

_____ Patient name or initials

_____ DOB

Maintenance Cycle 5 lasts 16 weeks. Therapy begins on Day 113 of Maintenance Cycle 4. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1 and 8	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, Creatinine ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m^2/dose BID	Days 1-7 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.17 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m^2/dose/day*	Days 1-112	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.17 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m^2/dose/week	Days 1, 8, 15, 22, 29, 36, 43, 50, 64, 71, 78, 85, 92, 99, and 106	**Omit Day 57 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 57	See Section 4.17 for administration guidelines **Note age-based dosing**	

_____Ht_____cm **Wt_____ kg** **BSA_____m^2**

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg		_____mg	a%, b, d	
		2							
		3							
		4							
		5							
		6							
		7							
		8	_____mg				_____mg		

		15					_____mg		

		22					_____mg		

		29					_____mg	a%, b	

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57				_____mg		a%, b, c	

		64					_____mg		

		71					_____mg		

		78					_____mg		

		85					_____mg	a%, b	

		92					_____mg		

		99					_____mg		

		106					_____mg		

		112							
		113	**Begin Cycle 6 (Section 4.18). Repeat cycles based on dose modifications for low counts or low platelets until 2½ yrs from diagnosis for both boys and girls.**						

% **Note**: Height (Ht) is only required at the beginning of this course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.18 Maintenance Arm LR-M – Cycle 6 (LR B-ALL Patients Randomized to Arm LR-M)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Please follow the dose modifications for low ANC or low platelets. Only oral Mercaptopurine and Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. IT MTX, VCR and DEX will be delivered as scheduled despite myelosuppression.

The administration schedule below describes one 16 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 7 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID) x 7 days

Dose is adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 1, 8, 15, 22, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, and 106. **Omit Day 29 dose as it coincides with IT MTX**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 112
Dose: 75 mg/m^2 once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details.

Methotrexate: Intrathecal (IT)
Day 29
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Maintenance consists of cycles every 16 weeks until a total duration of therapy of 2½ years from the date of diagnosis is reached for both boys and girls. Therapy may be stopped on that date if the 7 day dexamethasone is completed for the cycle (i.e. complete all 7 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm LR-M Cycle 6 is on the following page.

Following completion of Maintenance Arm LR-M Cycle 6, the next course (Maintenance Arm LR-M Cycle 7, Section 4.19) starts on Day 113.

4.18.1 Maintenance Arm LR-M (Cycle 6) – LR B-ALL Patients Randomized to Arm LR-M

_____ Patient name or initials

_____ DOB

Maintenance Cycle 6 lasts 16 weeks. Therapy begins on Day 113 of Maintenance Cycle 5. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1 and 8	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, Creatinine ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m^2/dose BID	Days 1-7 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.18 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m^2/dose/day*	Days 1-112	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.18 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m^2/dose/week	Days 1, 8, 15, 22, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, and 106	**Omit Day 29 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 29	See Section 4.18 for administration guidelines **Note age-based dosing**	

Ht _____ **cm** **Wt** _____ **kg** **BSA** _____ **m^2**

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg		_____mg	a%, b, d	
		2							
		3							
		4							
		5							
		6							
		7							
		8	_____mg				_____mg		

		15					_____mg		

		22					_____mg		

		29				_____mg		a%, b, c	

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57					_____mg	a%, b	

		64					_____mg		

		71					_____mg		

		78					_____mg		

		85					_____mg	a%, b	

		92					_____mg		

		99					_____mg		

		106					_____mg		

		112							
		113	**Begin Cycle 7 - last 10 weeks of Maintenance therapy (Section 4.19).**						

% **Note**: Height (Ht) is only required at the beginning of this course/cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.19 Maintenance Arm LR-M – Cycle 7 (LR B-ALL Patients Randomized to Arm LR-M)

AFTER ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET, ADDITIONAL PATIENTS CLASSIFIED AS AR AND LR B-ALL PATIENTS WILL NOT RECEIVE POST-INDUCTION TREATMENT ON AALL0932. FURTHER TREATMENT FOR THESE PATIENTS WILL BE UP TO THE DISCRETION OF THE TREATING PHYSICIAN. AR AND LR B-ALL PATIENTS RISK ASSIGNED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET WILL CONTINUE TO RECEIVE POST INDUCTION THERAPY ON THIS PROTOCOL.

Please follow the dose modifications for low ANC or low platelets. Only oral Mercaptopurine and Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. IT MTX, VCR and DEX will be delivered as scheduled despite myelosuppression.

The administration schedule below describes the last 10 weeks of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 7 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID) x 7 days

Dose is adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 1, 8, 15, 22, 29, 36, 43, 50, 57 and 64.
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 70
Dose: 75 mg/m^2 once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details.

Maintenance consists of cycles every 16 weeks until a total duration of therapy of 2½ years from the date of diagnosis is reached for both boys and girls. Therapy may be stopped on that date if the 7 day dexamethasone is completed for the cycle (i.e. complete all 7 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm LR-M Cycle 7 is on the following page.

4.19.1 Maintenance Arm LR-M (Cycle 7) – LR B-ALL Patients Randomized to Arm LR-M

_____ Patient name or initials

_____ DOB

Maintenance Cycle 7 lasts 10 weeks. Therapy begins on Day 113 of maintenance Cycle 6. This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1 and 8	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. Bilirubin, ALT, Creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m^2/dose BID	Days 1-7 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.19 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m^2/dose/day*	Days 1-70	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.19 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m^2/dose/week	Days 1, 8, 15, 22, 29, 36, 43, 50, 57 and 64		

_____Ht_____cm **Wt_____ kg** **BSA_____m^2**

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.					
		1	_____mg	_____mg _____mg	_____mg	_____mg	a%, b, c	
		2						
		3						
		4						
		5						
		6						
		7						
		8	_____mg			_____mg		

		15				_____mg		

		22				_____mg		

		29				_____mg	a%, b	

		36				_____mg		

		43				_____mg		

		50				_____mg		

		57				_____mg	a%, b	

		64				_____mg		

		70						
			End of therapy^					

% **Note**: Height (Ht) is only required at the beginning of this course/cycle.

^ Maintenance consists of cycles every 16 weeks until a total duration of therapy of 2½ years from the date of diagnosis is reached for both boys and girls. Therapy may be stopped on that date if the 7 day dexamethasone is completed for the cycle (i.e. complete all 7 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.20 Induction (35 Days) – DS SR B-ALL and DS B-LLy Patients

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cytarabine: Intrathecal (IT)
Given at the time of diagnostic lumbar puncture (LP) OR on Day 1.May be given up to 72 hours prior to the start of protocol therapy for patient convenience .
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	30 mg
2 – 2.99	50 mg
≥ 3	70 mg

For IT administration use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1, 8, 15 and 22
Dose: 1.5 mg/m^2/dose (maximum 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (may be given IV)
Days 1 - 28 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/day, divided BID) may be used temporarily as needed.

Pegaspargase: IV over 1 - 2 hours.
Day 4
Dose: 2,500 International Units/m^2/dose

Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

Special precautions:

1. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
2. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Methotrexate: Intrathecal (IT)
Days 8 and 29
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Leucovorin: PO
Days 10 - 11 and 31 - 32
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture.
Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture

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

Disease Evaluations During Induction for DS SR B-ALL Patients:

- Day 29: Bone marrow sample will be obtained for morphology and a 2 mL aliquot will be shipped to a COG-Approved ALL Flow Cytometry Laboratory for MRD determination.

Research Studies (for DS SR B-ALL patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (*if available for classification of newly diagnosed ALL patients*))

- Day 29: 5 mL of peripheral blood will be obtained and shipped to the COG ALL Molecular Reference Laboratory for studies of genomic variation and cell banking. ***This specimen is very important and should be obtained on all patients that have provided consent.***

NOTE: FOR DS SR B-ALL PATIENTS, IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY

Disease Evaluation for DS B-LLy Patients:

- Before starting therapy and on Day 29: patients will have a CT of the neck, chest, abdomen and pelvis, CXR, a PET scan, and a bone scan if indicated (Please refer to Section 7.1d for details).

Note: A PET scan is highly recommended but not required at diagnosis, at the end of Induction and if there are residual masses at the end of Consolidation.

Optional Research Studies for DS B-LLy Patients (see Section 14.0 for details)**:**

- If patient consents, paraffin embedded tissue will be submitted at diagnosis for FISH analysis.
- If patient consents, fresh tissue will be submitted at diagnosis for banking.
- Day 29: 5 mL of peripheral blood will be obtained and shipped to the COG ALL Molecular Reference Laboratory for studies of genomic variation. ***This specimen is very important and should be obtained on all patients that have provided consent.***

SEE SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE GUIDELINES.

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

For DS SR B-ALL and DS B-LLy: Following completion of Induction, the next course (Consolidation, Section 4.20) begins on Day 36 or when blood count parameters are met (whichever occurs later), based upon the patient's Day 29 MRD results.

Note: Following completion of Induction, DS B-LLy patients without PD (see Section 11.3 for definition) will be eligible to continue Consolidation therapy. **DS B-LLy patients with PD at end-Induction will be considered off protocol therapy.** Consolidation (Section 4.21) starts on Day 36 or when blood count parameters are met (whichever occurs later).

4.20.1 **Induction—DS SR B-ALL and DS B-LLy Patients (35 days)**
Leucovorin rescue will be given after each IT MTX

_____ Patient name or initials _____ DOB

Induction therapy lasts 5 weeks (35 days). See Section 4.20 for full treatment details. This Therapy Delivery Map is on one (1) page

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Intrathecal Cytarabine (IT ARAC)	IT	Age (yrs) Dose 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg	Given at time of diagnostic LP OR Day 1	See Section 4.20 for administration guidelines **Note age-based dosing**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 1, 8, 15 &22	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**
Dexamethasone (DEX)	PO (may give IV)	3 mg/m^2/dose BID	Days 1-28 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.20 for admin guidelines
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 4	**Note: pegaspargase should be administered on Day 4**. Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 8 & 29	See Section 4.20 for administration guidelines **Note age-based dosing**
Leucovorin (LCV)	PO	5 mg/m^2/dose q12 hrs	Days 10-11 & 31-32	48 & 60 hrs after each IT MTX. See Section 4.20 for administration guidelines

OBSERVATIONS

a. Hx, PE, Wt., Ht.
b. CBC/diff/platelets
c. BM eval[1]
d. PB sample[1]
e. CSF cell count, cytospin[2]
f. Bilirubin, Albumin ALT, Creatinine
g. Varicella titer
h. IgG
i. TPMT genotype and NUDT15[#]

DS B-LLy patients only

j CT (neck, chest, abdomen & pelvis), CXR, PET, bone scan if indicated.[3]
k Diagnostic biopsy/cytology[3]
l Biology/banking (optional) [4]
m Pregnancy test[5]

[1]See Section 7.1c for details
[2] Obtain with each IT administration
[3]See Section 7.1d for details
[4]See Sections 7.1d & 14.0 for details
[5]Only for patients of reproductive age

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Ht cm **Wt** kg **BSA** m^2

Date Due	Date Given	Day	IT ARAC ____mg	VCR ____mg	DEX (BID Dosing) ____mg ____mg	PEG-ASP ____IU	IT MTX ____mg	LCV ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below							
		-2/-1/0/LP*	____mg						(a%-c, e-g, h, [j-m]#)@	
		1		____mg	____mg ____mg					
		2								
		3								
		4				____IU				
		8		____mg			____mg		a%, b, e	
		9								
		10						____mg		
		11						____mg		
		15		____mg					a%, b, i	
		22		____mg					a%, b	
		28								
		29					____mg		a%, b, c**, d***, e	
		30								
		31						____mg		
		32						____mg		
		35							j#	
		36	Begin Consolidation (Section 4.21) on Day 36 or when blood count parameters are met (whichever occurs later). **DS B-LLy patients with PD at end-Induction are off protocol therapy.**							

* *On Day 1 **OR** at the time of diagnostic LP if ≤ 72 hrs from the start of protocol therapy*

% **Note**: Height (Ht) is only required at the beginning of this course.

#For DS B-LLy patients ONLY. **Note**: PET scans are highly recommended not required, and CXR is not required if CT chest is done (See Section 7.1d for details).

@ Baseline

** **Note: for DS SR B-ALL patients,** if Day 29 BM MRD sample is not obtained and shipped to a COG-Approved ALL flow cytometry lab, then the patient will not be eligible to continue on a COG ALL trial following completion of Induction therapy. # TPMT highly recommended for all subjects; NUDT15 is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects (See Section 5.9)

Day 29 PB sample should be shipped to the COG ALL Molecular Reference Laboratory for all DS SR B-ALL patients that consented to studies of genomic variation on AALL08B1 (or APEC14B1 (if open for the classification of newly diagnosed ALL patients) and DS B-LLy patients that consent on AALL0932 (see Section 14.0 for specimen shipping and handling). ***This specimen is very important.

DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR (1) ALL B-ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY (2) ALL DS B-LLY PATIENTS WHO DO NOT GO OFF PROTOCOL THERAPY AT END-INDUCTION. SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.21 Consolidation (28 days) –DS SR B-ALL and DS B-LLy Patients

FOR PATIENTS WITH DS SR B-ALL: CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY. DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF PROTOCOL THERAPY.

FOR PATIENTS WITH DS B-LLy: DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO DO NOT GO OFF PROTOCOL THERAPY AT THE END OF INDUCTION.

Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later) after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Therapy should be interrupted for patients with suspected or proven serious infection and resumed when the signs of infection have abated. Therapy should not be interrupted for simple fever, if there are no signs of serious infection.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1 ONLY
Dose: 1.5 mg/m^2/dose (maximum 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Mercaptopurine: PO
Days 1 - 28
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. Do not escalate dose based on blood counts during this cycle (see Section 5.8).

Methotrexate: Intrathecal (IT)
Days 1, 8, and 15
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Leucovorin: PO
Days 3 - 4, 10 - 11, 17 - 18
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture.

Leucovorin rescue will be given after IT MTX for patients with Down syndrome during all applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture. Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

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

For DS SR B-ALL and DS B-LLy: Following completion of Consolidation, the next course (Interim Maintenance I, Section 4.22) starts on Day 29 or when blood count parameters are met (whichever occurs later).

Note: Following completion of Consolidation, DS B-LLy patients who fail to achieve CR (see Section 11.3 for definitions), are off protocol therapy with the exception of DS B-LLy patients with bone primaries who will be considered CR if there is resolution of all surrounding soft tissue component by the end of Consolidation.

4.21.1 **Consolidation – DS SR B-ALL and DS B-LLy (28 days)** Leucovorin rescue will be given after each IT MTX	_____ _____ Patient name or initials DOB

Consolidation is 4 weeks (28 days). Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). See Section 4.21 for detailed therapy guidelines. This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Day 1 ONLY	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx/PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin & ALT e. IgG **DS B-LLy patients only** f CT (neck, chest, abdomen & pelvis), CXR, PET, bone scan (if bone involvement). ! Obtain with each IT administration. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mercaptopurine (MP)	PO	75 mg/m²/dose*	Days 1-28	See Section 4.21 & Appendix I for administration guidelines. *for suggested dose based on TPMT and NUDT15 status, see Section 5.9	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1, 8 & 15	See Section 4.21 for administration guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m²/dose q12 hrs	Days 3-4. 10-11 & 17-18	48 & 60 hrs after each IT MTX. See Section 4.21 for administration guidelines	

Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR _____mg	MP _____mg	IT MTX _____mg	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	_____mg	_____mg	_____mg		a, b, c, d, e	
		2						
		3				_____mg		
		4				_____mg		

		8			_____mg		c	
		9						
		10				_____mg		
		11				_____mg		

		15			_____mg		c	
		16						
		17				_____mg		
		18				_____mg		

		28					f^	
		29	**Begin next course (Interim Maintenance I, Section 4.22) on Day 29 or when blood count parameters are met (whichever occurs later). Note: DS B-LLy patients without CR at end-Consolidation are off protocol therapy, except patients with bone primaries who are considered CR if there is resolution of all surrounding soft tissue component by the end of Consolidation.**					

^ For DS B-LLy patients ONLY. **Note**: PET scans for residual masses are highly recommended, not required, and CXR is not required if CT chest is done (See Section 7.1d for details).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.22 Interim Maintenance I (56 days) - DS SR B-ALL and DS B-LLy Patients

Criteria to Start Interim Maintenance I

Begin IM on Day 29 of Consolidation or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later.

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

A) If ANC is < 500/µL or platelets < 50,000/µL, hold all chemotherapy and repeat blood counts in 4 days.
   1. In 4 days, if ANC ≥ 500/µL and platelets ≥ 50,000/µL, give same dose of methotrexate as previous cycle.
   2. In 4 days, if ANC is still < 500/µL or platelets < 50,000/µL, give VCR (and IT MTX if Day 31) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and IV MTX if counts are adequate.
      a. If after 7 days, ANC ≥ 500/µL and platelets ≥ 50,000/µL, reduce dose of MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A-C.
      b. If after 7 days ANC is still < 500/µL or platelets < 50,000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL. When ANC ≥ 500/µL and platelets ≥ 50,000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A - C.

B) If ANC ≥ 500/µL but < 750/µL and/or platelets ≥ 50,000/µL but < 75,000/µL, give same dose of MTX as previously (i.e. no escalation).

C) If ANC ≥ 750/µL and platelets ≥ 75,000/µL escalate MTX by 50 mg/m^2/dose.

D) Do not escalate MTX dose and resume at 80% of last dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume escalation as per A - C.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

Days 1, 11, 21, 31, and 41

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

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Methotrexate: IV over 2-5 minutes (undiluted) or over 10-15 minutes (diluted).

Days 1, 11, 21, 31 and 41

Starting dose of 100 mg/m^2/dose; **thereafter, escalate by 50 mg/m^2/dose**

Methotrexate: Intrathecal (IT)
Day 31 ONLY
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Leucovorin: PO
Days 33 - 34
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture

Leucovorin rescue will be given after IT MTX for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture

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

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Interim Maintenance I is on the next page.

For DS SR B-ALL and DS B-LLy: Following completion of Interim Maintenance I, the next course (Delayed Intensification, Section 4.23) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.22.1 **Interim Maintenance I– DS SR B-ALL and DS B-LLy (56 days)**

Leucovorin rescue will be given after each IT MTX

_____ _____
Patient name or initials DOB

Interim Maintenance I begins when ANC ≥ 750/µL and platelets ≥ 75,000/µL. This course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1) page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT & Creatinine e. IgG **B-LLy patients only** f. CT (neck, chest, abdomen & pelvis), CXR, bone scan (if bone involvement). ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	IV over 2-5 min (undiluted) or 10-15 min (diluted)	Starting dose 100 mg/m² **& escalate by 50 mg/m²/dose**	Days 1, 11, 21, 31 & 41	Discontinue escalation & resume @ 80% of last dose if delay is necessary for myelosuppression and/or Grade 3 mucositis See Section 4.22 for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 31 ONLY	See Section 4.22 for administration guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m²/dose q12 hrs	Days 33-34	48 & 60 hrs after each IT MTX. See Section 4.22 for administration guidelines	

Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR ____mg	IV MTX ____mg *(escalating dose)*	IT MTX ____mg	LCV ____mg	Studies	Comments (Include any held doses, or dose modifications
			Enter calculated dose above and actual administered dose below.					
		1	____mg	____mg			a%, b, d, e	

		11	____mg	____mg			a%, b, d	

		21	____mg	____mg			a%, b, d	

		31	____mg	____mg	____mg		a%, b, c, d,e	
		32						
		33				____mg		
		34				____mg		

		41	____mg	____mg			a%, b, d	

		56					f^	
		57	**Begin next course (Delayed Intensification, Section 4.23) on Day 57 or when blood count parameters are met (whichever occurs later)**					

% **Note**: Height (Ht) is only required at the beginning of this course

^ For B-LLy patients ONLY. **Note**: CXR is not required if CT chest is done (See Section 7.1d for details).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.23 Delayed Intensification (56 days) - DS SR B-ALL and DS B-LLy Patients

Criteria to Start Delayed Intensification
Delayed intensification begins on Day 57 of Interim Maintenance I, or when ANC ≥ 750/μL and platelets ≥ 75,000/μL, whichever occurs later.

Interruption and/or Modifications of Therapy
All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 1 - 28 or Days 30 - 43, but Day 29 does not begin unless ANC ≥ 750/μL and platelets ≥ 75,000/μL. Therapy interruptions should be made-up. In case of delays of 3 weeks or longer, notify the Study Chair.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Dexamethasone: PO (may give IV)
All patients, regardless of age or response, receive discontinuous dexamethasone.
Days 1 - 7 and 15 - 21
Dose: 5 mg/m^2/dose BID (i.e., total daily dose: 10 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m^2/day, divided BID) may be used temporarily as needed.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1, 8 and 15
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

DOXOrubicin: IV push/infusion over 1 - 15 minutes
Days 1, 8 and 15.
Dose: 25 mg/m^2/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1 - 15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein or central venous access device.

Pegaspargase: IV over 1 - 2 hours.
Day 4
Dose: 2,500 International Units/m^2/dose
Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

Special precautions:

1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Cyclophosphamide: IV over 30 - 60 minutes
Day 29
Dose: 1,000 mg/m^2/dose

Hydrate according to institutional guidelines. Suggested hydration: Pre-hydrate using fluids containing at least 0.45% NaCl. Achieve urine specific gravity of ≤ 1.010 prior to start of cyclophosphamide. Continue hydrating at a rate of 125 mL/m^2/hour IV/PO for at least 8 hours after cyclophosphamide administration.

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

Thioguanine: PO
Days 29 - 42.
Dose: 60 mg/m^2/dose/once daily*

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

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

Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details.

Cytarabine: IV over 1 - 30 minutes or subcutaneous
Days 29 - 32 and 36 - 39
Dose: 75 mg/m^2/dose/day

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

Methotrexate: Intrathecal (IT)
Days 1 and 29
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Leucovorin: PO
Days 3 - 4 and 31 - 32
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture

Leucovorin rescue will be given after IT MTX for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture

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

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

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

For DS SR B-ALL and DS B-LLy: Following completion of Delayed Intensification, the next course (Interim Maintenance II, Section 4.24) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.23.1a **Delayed Intensification — DS SR B-ALL and DS B-LLy (56 days)**
Leucovorin rescue will be given after each IT MTX

_____ Patient name or initials _____ DOB

Delayed Intensification is 8 weeks (56 days). Begin DI on Day 57 of IM I or when ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later. See Section 4.23 for detailed therapy interruption guidelines. This therapy delivery map is on **two (2) pages**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (may give IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID See Section 4.23 for administration guidelines	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin [1] d. Bilirubin, ALT, Creatinine e. IgG f. Echocardiogram[2] [1] Obtain with each IT administration [2] Prior to first dose of doxorubicin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 1, 8 & 15	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m^2/dose	Days 1, 8 & 15	See Section 4.23 for guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 4	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Day 29	See Section 4.23 for guidelines	
Thioguanine (TG)	PO	60 mg/m^2/dose/day	Days 29-42	See Section 4.23 & Appendix II for guidelines *for suggested dose based on TPMT and NUDT15 status, see Section 5.11	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose/day	Days 29-32 & 36-39		
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1 & 29	See Section 4.23 for administration guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m^2/dose q12 hrs	3-4 & 31-32	48 & 60 hrs after each IT MTX. See Section 4.23 for administration guidelines	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	DEX ____mg ____mg	VCR _____mg	DOXO _____mg	PEG-ASP _____IU	CPM* _____mg	TG* _____mg	ARAC* _____mg	IT MTX _____mg	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.										
		1	____mg ____mg	_____mg	_____mg					_____mg		a%, b, c, d, e, f^	
		2											
		3									_____mg		
		4				_____IU					_____mg		
		5											
		6											
		7											
		8		_____mg	_____mg							a%, b	

		15	____mg ____mg	_____mg	_____mg							a%, b	
		16											
		17											
		18											
		19											
		20											
		21											
		22											
		---	**This Therapy Delivery map continues on the next page.**										

% **Note**: Height (Ht) is only required at the beginning of this course.
***** Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy ^ Prior to first dose of doxorubicin
SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.23.1b **Delayed Intensification — DS SR B-ALL and DS B-LLy (56 days) -Continued**
Leucovorin rescue will be given after each IT MTX

_____ Patient name or initials _____ DOB

*Delayed Intensification is 8 weeks (56 days). Begin DI on Day 57 of IM I or when ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later. See Section 4.23 for detailed therapy interruption guidelines. This therapy delivery map is on **two (2) pages**.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (may give IV)	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID See Section 4.23 for administration guidelines	a. Hx, PE, Wt b. CBC/diff/platelets c. CSF cell count, cytospin [1] d. Bilirubin, ALT, Creatinine e. IgG f. Echocardiogram[2] [1] Obtain with each IT administration [2] Prior to first dose of doxorubicin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 8 & 15	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m²/dose	Days 1, 8 & 15	See Section 4.23 for guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m²/dose	Day 4	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m²/dose	Day 29	See Section 4.23 for guidelines	
Thioguanine (TG)	PO	60 mg/m²/dose/day	Days 29-42	See Section 4.23 & Appendix II for guidelines *for suggested dose based on TPMT and NUDT15 status, see Section 5.11	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m²/dose/day	Days 29-32 & 36-39		
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1 & 29	See Section 4.23 for administration guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m²/dose q12 hrs	3-4 & 31-32	48 & 60 hrs after each IT MTX. See Section 4.23 for administration guidelines	

Ht _____ cm Wt _____ kg BSA _____ m²

Date Due	Date Given	Day	DEX ____mg ____mg	VCR ____mg	DOXO ____mg	PEG-ASP ____IU	CPM* ____mg	TG* ____mg	ARAC* ____mg	IT MTX ____mg	LCV ____mg	Studies	Comments (Include any held doses, or dose modifications)
		29*					____mg	____mg	____mg	____mg		a%, b, c, d, e	
		30											
		31									____mg		
		32									____mg		

		36							____mg			b	
		37											
		38											
		39											

		42											
		43											

		50											

		56											
		57	**Begin next course (Interim Maintenance II, with IV MTX Section 4.24) on Day 57 or when blood count parameters are met (whichever occurs later).**										

% **Note**: Height (Ht) is only required at the beginning of this course.

***** Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.24 Interim Maintenance II (56 days) - DS SR B-ALL and DS B-LLy Patients

Criteria to Start Interim Maintenance II
Begin IM II on Day 57 of DI, or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later.

Interruption and/or Modification of Therapy
All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

A) If ANC is <500/µL or platelets < 50,000/µL, hold all chemotherapy and repeat blood counts in 4 days.
   1. In 4 days, if ANC ≥ 500/µL and platelets ≥ 50,000/µL, give same dose of methotrexate as previous cycle.
   2. In 4 days, if ANC is still < 500/µL or platelets < 50,000/µL, give VCR (and IT MTX if Day 31) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and IV MTX if counts are adequate.
      a. If after 7 days, ANC ≥ 500/µL and platelets ≥ 50,000/µL, reduce dose of MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A-C.
      b. If after 7 days ANC is still < 500/µL or platelets < 50,000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL. When ANC ≥ 500/µL and platelets ≥ 50,000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A - C.

B) If ANC ≥ 500/µL but < 750/µL and/or platelets ≥ 50,000/µL but < 75,000/µL, give same dose of MTX as previously (i.e. no escalation).
C) If ANC ≥ 750/µL and platelets ≥ 75,000/µL escalate MTX by 50 mg/m^2/dose.
D) Do not escalate MTX dose and resume at 80% of last dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume escalation as per A - C.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for
special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1, 11, 21, 31, and 41.
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Methotrexate: IV over 2-5 minutes (undiluted) or over 10-15 minutes (diluted).
Days 1, 11, 21, 31 and 41
Starting dose is two-thirds of the maximum tolerated dose attained in Interim Maintenance I. For example, if a patient has toxicity at 250 mg/m² on Interim Maintenance I, the starting dose for Interim Maintenance II will be two-thirds of 200 mg/m^2 (or 130 mg/m^2) IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted). Subsequent doses will be escalated by 50 mg/m² every 10 days (± 2 days) for 4 doses, to toxicity Days 11, 21, 31 and 41.

Methotrexate: Intrathecal (IT)
Days 1 and 31
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

Leucovorin: PO
Days 3 - 4 and 33 - 34
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture

Leucovorin rescue will be given after IT MTX for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture

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

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

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

For DS SR B-ALL and DS B-LLy: Following completion of Interim Maintenance II, the next course (Maintenance Arm DS, Section 4.25) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.24.1 Interim Maintenance II - DS SR B-ALL and DS B-LLy (56 days)

Leucovorin rescue will be given after each IT MTX

_____
_____
Patient name or initials DOB

Interim Maintenance II begins on Day 57 of DI or when ANC ≥ 750/µL and platelets ≥ 75,000/µL whichever occurs later. This course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1) page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[1] d. Bilirubin, ALT, Creatinine. e. IgG [1] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	IV over 2-5 min (undiluted) or 10-15 min (diluted)	____mg/m²/dose*	Days 1, 11, 21, 31 & 41	*Starting dose for IM II is two-thirds of the maximum tolerated dose attained in Interim Maintenance I (see Section 4.23 for details). Thereafter, **escalate by 50 mg/m²/dose** See Section 4.23 for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1 and 31	See Section 4.23 for administration guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m²/dose q12 hrs	3-4 & 33-34	48 & 60 hrs after each IT MTX. See Section 4.23 for administration guidelines	

Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR ____mg	IV MTX ____mg *(escalating dose)*	IT MTX ____mg	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual administered dose below.					
		1	____mg	____mg	____mg		a%, b, c, d, e	
		2						
		3				____mg		
		4				____mg		

		11	____mg	____mg			a%, b, d	

		21	____mg	____mg			a%, b, d	

		31	____mg	____mg	____mg		a%, b, c, d, e	
		32						
		33				____mg		
		34				____mg		

		41	____mg	____mg			a%, b, d	

		56						
		57	**Begin next course (Maintenance Arm DS, Section 4.25) on Day 57 or when blood count parameters are met (whichever occurs later)**					

% **Note**: Height (Ht) is only required at the beginning of this course.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.25 Maintenance Arm DS - DS SR B-ALL and DS B-LLy Patients

DS SR-ALL and DS B-LLy patients will be non-randomly assigned to Maintenance treatment Arm DS:

- Vincristine/dexamethasone pulses at **12 week** intervals,
- IT methotrexate every 12 weeks
- Oral methotrexate at **20 mg/m^2/week**.

Criteria to begin Maintenance

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and dexamethasone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of cycles every 12 weeks until a total duration of therapy of 2 years is reached for both female and male patients from the start of Interim Maintenance I, which differs from the gender-based duration of therapy in children without DS. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

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

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO
Days 1 - 5(do not taper).
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Dose is adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/dose/day, divided BID) may be used temporarily as needed.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**
Dose: **20 mg/m^2/dose** weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. For ease of swallowing, methotrexate injection can be administered orally (see drug monograph).

Mercaptopurine: PO
Days 1 - 84
Dose: 75 mg/m^2/dose daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

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

The liquid or tablet formulation may be used. Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.8 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5 - 10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

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

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

The therapy delivery map (TDM) for Maintenance Arm DS is on the following page.

4.25.1 Maintenance Arm DS - DS SR B-ALL and DS B-LLy

_____ Patient name or initials _____ DOB

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL, (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Sections 4.25 and 5.9 for details. This Therapy Delivery Map is on **one (1) page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Day 1	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT & Creatinine e. IgG **DS B-LLy patients only** f. CT (neck, chest, abdomen & pelvis), CXR, bone scan (if bone involvement)^ ! Obtain with each IT administration ^Please refer to Section 7.1d for details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	Days 1-5 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.25 for administration guidelines	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day*	Days 1-84	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.25 & Appendix I for administration guidelines	
Methotrexate (MTX)	PO	**20 mg/m²/dose/week**	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	**Omit Day 1 dose as it coincides with IT MTX**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Day 1	See Section 4.25 for administration guidelines **Note age-based dosing**	

Enter Cycle # _____Ht_____cm Wt_____ kg BSA_____m²

Date Due	Date Given	Day	VCR _____mg	DEX _____mg _____mg	MP _____mg	IT MTX _____mg	PO MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.						
		1	_____mg	_____mg _____mg	_____mg	_____mg		a%, b, c, d, e	
		2							
		3							
		4							
		5							

		8					_____mg		

		15					_____mg		

		22					_____mg		

		29					_____mg	a%, b, e	

		36					_____mg		

		43					_____mg		

		50					_____mg		

		57					_____mg	a%, b, e	

		64					_____mg		

		71					_____mg		

		78					_____mg		

		84						f^	
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs (both male and female) from start of IM I**						

% **Note**: Height (Ht) is only required at the beginning of each course/cycle.

^At completion of Maintenance therapy. **Note**: CXR is not required if CT chest is done (see Section 7.1d for details).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE

5.0 DOSE MODIFICATIONS FOR TOXICITIES

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

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

Allergy

Local Allergic Reactions (inflammation at injection site, swelling): Continue pegaspargase 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 Grade 2 or higher allergic reactions as defined by the CTCAE v4.0

Note: Premedication with antihistamines to decrease the risk of overt allergy symptoms has been discouraged in the past since anti-histamine use may mask the appearance of systemic allergy and fail to alert the provider of the presence of asparaginase neutralizing antibodies, which renders asparaginase therapy ineffective. Asparaginase activity assays are now commercially available so that in the face of premedication; if allergy is suspected, or; if a provider seeks to monitor asparaginase therapy, a sample can be sent to determine activity and evaluate the patient for the presence of neutralizing antibodies. In the event of severe systemic or recurrent local allergic reaction, or if activity level is not detectable in an appropriately drawn sample, Erwinia asparaginase (now FDA-approved for this indication) should be substituted.

Anaphylaxis

Discontinue pegaspargase if the patient develops Grade 3 anaphylaxis as defined by CTCAE v4.0 (symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; allergy-related edema/angioedema; hypotension). If this occurs, Erwinia asparaginase (now FDA-approved for this indication) should be substituted.

Erwinia asparaginase 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.[50,51] 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.[52] Current COG trials have adopted pegaspargase as the preparation of choice, based on the results of CCG 1962.[53] 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 for replacement of Erwinia asparaginase for either native or pegaspargase utilizing the following schedule:

Phase(s) of Treatment	Replacement Schedule for Erwinia asparaginase[#]
Any Phase	25,000 IU/m^2/dose IM or IV M/W/F x 6 doses for each dose of pegaspargase

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

To replace a dose of intravenous pegaspargase that was discontinued during the infusion due to an allergic reaction, the following recommendations may be used to guide patient care.

In the event that a pegaspargase infusion is discontinued for an allergic reaction, regardless of amount received, substitution with *Erwinia* asparaginase should begin approximately 48 hours after pegaspargase has been discontinued and preferably to coincide with the recommended Monday/Wednesday/Friday administration schedule detailed above in patients who are clinically stable. Up to 6 doses of *Erwinia* asparaginase may be administered, as tolerated, to replace the incomplete intravenous pegaspargase dose. Of note, *Erwinia* asparaginase is recommended only for pegaspargase hypersensitivity reactions, and not for pancreatitis, hepatitis, coagulation abnormalities, or other non-hypersensitivity toxicities associated with pegaspargase. To best suit the needs of each individual patient, additional modifications to these recommendations may be made at the discretion of the treating physician.

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 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 (abdominal pain > 72 hours and ≥ Grade 3 amylase elevation (≥ 2.0x ULN). 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 antithrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing LMWH or antithrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate. For significant thrombosis, not line related, consider evaluation for inherited predisposition to thrombosis.

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

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

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 1,000 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) IV

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 Delayed Intensification (DI) has started do not interrupt for uncomplicated myelosuppression; do hold for ANC < 500/µL and severe infection. Do make up missed doses.

5.4 Intrathecal Cytarabine

Do not withhold dose given on Day 1 of Induction in front-line protocols

5.5 Doxorubicin (Anthracyclines)

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

Doxorubicin is contraindicated in congestive heart failure and cardiac dysfunction (SF < 27%).
Resuming Doxorubicin therapy depends on the cause of the cardiac dysfunction and the results of further cardiac evaluation. Notify Study Chair if patient cannot have further anthracycline therapy.

Severe infection or severe mucositis (Grade 3 - 4)
Therapy should be interrupted for patients who are febrile, neutropenic and have proven or suspected serious infection and resumed when the signs of infection have resolved

Myelosuppression: Do not hold for myelosuppression on Days 8 and 15.

Hyperbilirubinemia:[54]

Direct Bilirubin	% Dose Reduction
< 1.2 mg/dl	Full dose
1.2 – 3.0 mg/dl	50%
3.1 – 5.0 mg/dl	75%
> 5.0 mg/dl	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

Extravasation:
In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see

https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG guidelines.

5.6 Intrathecal Methotrexate

Systemic toxicity: The dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Instead, leucovorin may be used at a dose of 5 mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC < 500/μL) or mucositis. Do not administer leucovorin solely to prevent myelosuppression. For patients with Down syndrome, leucovorin should be administered after every dose of IT MTX during ALL phases of therapy EXCEPT Maintenance.

Dose modifications following an episode of acute neurotoxicity:
Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.[55-57] These toxicities are poorly understood and currently it is impossible to predict who will suffer these complications. In addition, there are no data clearly linking the occurrence of an acute neurotoxic event with an increased risk of long-term neurocognitive dysfunction, nor do changes present on MRI at the time of an acute event clearly correlate with or predict outcome.[57-62] It is clear however, that CNS prophylaxis is a mandatory component of curative therapy for children with ALL. Effective prophylaxis generally takes 2 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, ARAC and hydrocortisone). Certain protocols, for example BFM 2000,[63] include fewer doses of IT MTX, with an acceptably low frequency of CNS relapse, but the backbone of the BFM therapies is not the same as those currently used by the Children's Oncology Group. The exclusive use of IT ARAC has not been studied or described in the context of ALL therapy nor can one demonstrate the safety of omitting multiple doses of IT therapy without concomitant use of cranial irradiation or high dose methotrexate.

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

Following an acute neurotoxic event, a history and physical exam should guide the differential diagnosis. A neurology consult may be of value and should be considered. Seizures and other transient events may be linked to fever, infection, encephalitis, meningitis, hypertension, electrolyte disturbance, hypoglycemia, trauma, intracranial hemorrhage or thrombosis, narcotic withdrawal, illicit drug use, or other causes in addition to the direct side effects of chemotherapy. Appropriate laboratory studies may include, but are not limited to, blood cultures, a CBC, electrolytes, including glucose, calcium, magnesium and phosphorus, renal and liver function studies and/or an examination of the CSF. Imaging studies may include a CT scan and/or an MRI. The CT is commonly normal, in the absence of stroke, but if calcifications are present, this finding may be indicative of a more severe mineralizing leukoencephalopathy.[64] MRI abnormalities may be pronounced, but transient. Posterior reversible encephalopathy may be present on MR with extensive diffusion abnormalities, but these do not appear to correlate with subsequent demyelination or gliosis.[65-67] Additional studies, including MR angiography and/or venogram should be considered, if clinically indicated (e.g. focal deficits).

Many acute events, seizures or episodes of transient hemiparesis, are temporally related to the administration of intrathecal therapy, commonly 9 to 11 days after the IT administration.[68] 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 1 dose of IT MTX, or triple IT therapy. It is also reasonable to include leucovorin rescue at a dose of 5 mg/m^2 q 12 hrs x 2 doses beginning 48 hours after the LP. This pattern of rescue was associated with a clear diminution in the incidence of acute neurotoxicity in 1 case series.[68] There have been questions about potential interference of leucovorin with the efficacy of the IT MTX, but there is little data to support or refute this position. Moreover, the administration 48 hours later would minimize any potential interference. If the event does not recur, resumption of standard therapy should be considered, following 1 modified or omitted IT dose. In the face of multiply recurrent events, or evidence of progressive encephalopathy, another evaluation is warranted and the treating physician may consider a more prolonged or definitive change in therapy. These decisions are extremely difficult and may hinge on an individual's view of the importance of quality of life versus an increase in the risk of relapse. Since the greatest impact of CNS prophylaxis occurs early in therapy, the timing of these events may also influence clinical decisions. Cranial radiation has been suggested as an alternative to continued IT therapy though much of the literature on long-term neurocognitive dysfunction supports a more deleterious effect from CRT than IT therapy.[69-72] Dramatic deviations from protocol recommended therapy might result in the child being taken off protocol therapy.

The use of dextromethorphan (DM) has been suggested as a neuroprotectant, capable of preventing NMDA mediated neurotoxicity without prohibitive toxicity. Low dose therapy has been recommended, in part, based on data suggesting that DM is concentrated in brain relative to serum. However, the literature on the use of DM supports a tight dose response relationship, with the likelihood of sparing an initially unaffected area, following ischemic damage, linked to dose, in both clinical trials and animal models of CNS ischemia.[73-76] At doses thought to be therapeutic, side effects have included nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. In addition, Hollander et al[77] have raised concerns about the potential deleterious effects of long-term NMDA receptor blockade on memory because hippocampal long-term potentiation is dependent on the activation of the NMDA receptor. Thus in the absence of a clinical trial there are few data to support the addition of DM.

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.

5.7 IV Methotrexate

5.7.1 IV Methotrexate in Interim Maintenance (AR B-ALL, LR B-ALL randomized to Arm LR-C, DS SR B-ALL, B-LLy and DS B-LLy)

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 dose
10 – 20 X ULN for 2 consecutive doses	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at the dose that was previously administered 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 serology. Consider liver biopsy before additional therapy given.

* Please see COG Supportive Care Guidelines at: https://members.childrensoncologygroup.org/index.php/cog-supportive-care-guidelines for TMP/SMX substitutions.

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

Nephrotoxicity: Postpone course if serum creatinine is > 1.5 x baseline or GFR creatinine clearance is < 65 mL/1.73m²/minute.

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

Myelosuppression:

A) If ANC is < 500/µL or platelets < 50,000/µL, hold all chemotherapy and repeat blood counts in 4 days.
   1. In 4 days, if ANC ≥ 500/µL and platelets ≥ 50,000/µL, give same dose of methotrexate as previous cycle.
   2. In 4 days, if ANC is still < 500/µL or platelets < 50,000/µL, give VCR (and IT MTX if Day 31) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and MTX if counts are adequate.
   a. If after 7 days, ANC ≥ 500/µL and platelets ≥ 50,000/µL, reduce dose of MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A - C.
   b. If after 7 days ANC is still < 500/µL or platelets < 50,000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL. When ANC ≥ 500/µL and platelets ≥ 50,000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A - C.

B) If ANC ≥ 500/µL but < 750/µL and/or platelets ≥ 50,000/µL but < 75,000/µL, give same dose of MTX as previously (i.e., no escalation).
C) If ANC > 750/µL and platelets > 75,000/µL escalate MTX by 50 mg/m^2.

5.7.2 IV Intermediate Dose (ID – 1,000 mg/m^2) Methotrexate and Leucovorin Rescue in Consolidation for B-ALL patients randomized to Arm LR-M.

Day 1 of Consolidation begins 1 week after the end of Induction regardless of counts.

However, oral 6-MP should not be started until ANC ≥ 500/µL and platelets ≥ 75,000/µL.

If the start of oral 6-MP is delayed, DO NOT "make up" missed doses. It is recommended to repeat a CBC every 2 to 3 days and start oral 6-MP when counts meet criteria; deliver initial IV MTX 2 weeks after end of Induction (if count parameters) met regardless of the length of 6-MP administration.

Each MTX infusion is to begin when ANC ≥ 500/µL and platelets ≥ 75,000/µL; ALT < 20 x upper limit of normal and bilirubin and creatinine normal for age.

After an IV dose of MTX is given continue with oral 6-MP for the next 3 weeks even in the face of uncomplicated myelosuppression.

When a course of IV MTX is due and ANC < 500/µL and/or platelets < 75,000/µL, delay IV MTX administration and HOLD 6-MP until ANC ≥ 500/µL and platelets ≥ 75,000/µL, then restart at 100% dosing.

When a subsequent course of IV MTX is due and ANC < 500/µL and/or platelets < 75,000/µL, delay IV MTX administration and HOLD 6-MP until recovery and then restart at 75% dose.

Also consider TMP/SMX as possible cause of neutropenia. Consider discontinuing TMP/SMX in favor of an alternative approach to pneumocystis prophylaxis, as per COG Supportive Care Guidelines (see https://members.childrensoncologygroup.org/prot/reference_materials.asp.

When IT therapy and ID 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 hour 0 being the start of the MTX infusion).

Hold TMP-SMX on the days of ID MTX infusion and for at least 72 hours after the start of the ID MTX infusion and until the MTX level is less than 0.4 µM. *In the presence of delayed clearance continue to hold TMP-SMX until MTX level is less than 0.1 µM.*

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

Pre-hydrate with D_5 ¼ NS with 30 mEq/L sodium bicarbonate at 100 mL/m^2/hour until urine specific gravity is ≤ 1.010 and urine pH is ≥ 6.5 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters.

Continue hydration and alkalinization until plasma MTX level is < 0.2µM. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 µM (see below for details). A bicarbonate bolus (25 mEq/m^2 over 15 minutes) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration.

Hours 24, (36), (42) and 48: Draw MTX level and serum creatinine; NOTE: the 36 & 42 hour levels are only drawn if needed (see below)

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.

If the 24 hour level is ≤ 20 μM draw the next level at hour 48 and continue with hydration at 100 mL/m^2 and continue leucovorin at 10 mg/m^2 q 6h until MTX level < 0.2 μM

If the 24 hour level is > 20 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 described below and repeat the level with a serum creatinine at hour 36. **If the 36 hour level is ≥ 3 micromolar**, increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also **consider Carboxypeptidase G$_2$ (glucarpidase) if 36 hour MTX level exceeds 10 micromolar.**

Management of the patient with markedly delayed MTX clearance: If MTX level ≥ 2 μM at Hour 48, increase hydration to 200 mL/m^2/hour post chemotherapy hydration. Maintain urine pH > 6.5. Continue leucovorin at 100 mg/m^2 q 6hr. Check levels every 12 to 24 hours and discontinue leucovorin as soon as MTX level is < 0.1 μM. Do not give additional MTX if renal function is not normal. If it is, decrease next MTX doses by 50% with standard rescue and hydration at 200 mL/m^2/hour post chemotherapy hydration. If tolerated without delayed excretion, increase dose of MTX by 25% (of the original MTX dose) for each course until administration of full dose MTX is achieved

For MTX levels that exceed these expected values modify the rescue regimen as noted below and increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly, at any time point, assure appropriate urine pH and urine volume as above and draw a 42 hour level. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase.

DO NOT EXTEND leucovorin or modify subsequent courses unless the patient experienced Grade 3 or 4 mucositis or > 1 week delay in administration of chemotherapy. However, if patient again has delayed clearance, treat as in section above.

For patients with marked delayed clearance (48 hour level ≥ 2 μM) or who had clinical toxicity in a prior course (≥ Grade 2 mucositis or > 1 week delay in administration of chemotherapy) 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.

(36 hr MTX level) (if needed)+	42 hr MTX level (if needed)+	48 hr MTX level	Hydration and Leucovorin Rescue++
	< 0.5 μM	< 0.2 μM	Continue with hydration at 100 mL/m^2 until plasma MTX level is < 0.2 μM. Continue leucovorin at 10 mg/m^2 q 6 hr x 2 doses given at hours 42 and 48 after the start of the MTX infusion.

			If the patient has had clinical toxicity (see definition below) on a prior cycle, consider giving the 54 hour dose of leucovorin
	0.51 to < 2.5 µM	0.21 to < 2 µM	Increase hydration to 200 mL/m^2 until plasma MTX level is < 0.2 µM. Continue leucovorin at 10 mg/m^2 q 6hr until MTX level < 0.2 µM (draw q 6-24 hr).
≥ 3 µM	≥ 2.5 µM	≥ 2 µM	Increase hydration to 200 mL/m^2 until plasma MTX level is < 0.2 µM. Increase to leucovorin to 100 mg/m^2 q 6 hr until MTX level < 0.1 µM (draw q 6-24 hr). Consider glucarpidase

+ Only required if 24 hr level is > 20 µM. See above for guidelines

++ 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 < 0.5 and/or < 0.2 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, delay MTX for up to 2 weeks until these parameters are met. Do not give IDMTX to a patient with this degree of renal impairment, assuming that prolonged excretion can be managed with glucarpidase. If IDMTX is delayed more than 2 weeks, omit this dose and resume with the next scheduled dose if parameters are met. Patients who must omit more than 1 course of IDMTX may remain on study.

NOTE: For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G_2, Voraxaze™).[78,79] ASD Healthcare is the sole supplier of glucarpidase in the US. 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. 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 may remain on study, and may receive further courses of IDMTX at investigator discretion if renal function is adequate as per parameters above.

Liver Dysfunction: Samples for the determination of ALT value must be drawn 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 dose
10 – 20 X ULN for 2 consecutive doses	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 serology. Consider liver biopsy before additional therapy given.

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

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

Mucositis: For Grade 3 - 4 mucositis, withhold IV MTX until resolved. Increase leucovorin rescue following the next course from 3 to 5 doses on a q6 hr schedule. If subsequent course is not associated with Grade 3 - 4 mucositis, attempt to decrease the leucovorin. If mucositis recurs despite the extended leucovorin, decrease the dose of MTX by 25%, increase hydration to 200 mL/m^2/hr and continue increased leucovorin as above. Should subsequent courses be well tolerated, use a stepwise approach to resuming a standard approach to drug delivery. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Myelosuppression:

- After an IV dose of MTX is given, continue with oral 6-MP for the next 3 weeks even in the face of uncomplicated myelosuppression.
- When a course of IV MTX is due and ANC < 500/µL and/or platelets < 75,000/µL, delay IV MTX administration and HOLD 6-MP until ANC ≥ 500/µL and platelets ≥ 75,000/µL, then restart 6-MP at 100% dosing.
- When a subsequent course of IV MTX is due and ANC < 500/µL and/or platelets < 75,000/µL, delay IV MTX administration and HOLD 6-MP until count recovery and then restart 6-MP at 75% dose.
- Also consider TMP/SMX as possible cause of neutropenia. Consider discontinuing TMP/SMX in favor of an alternative approach to pneumocystis prophylaxis, as per COG Supportive Care Guidelines (see https://members.childrensoncologygroup.org/prot/reference_materials.asp.)
- Consider TPMT testing at diagnosis and also consider TPMT genotyping in patients encountering significant myelosuppression during Consolidation therapy.
- If prolonged myelosuppression (ANC < 500/µL or platelets < 75,000/µL for more than 7 days) recurs with these modifications then reduce methotrexate dose by 20%.

5.8 PO 6-Mercaptopurine (6-MP) - Consolidation

5.8.1 PO 6-mercaptopurine (6-MP) - Consolidation for AR B-ALL, LR B-ALL randomized to Arm LR-C, DS SR B-ALL, B-LLy and DS B-LLy

For low blood counts:

a) ANC ≥ 750/µL and < 1,000/µL and/or platelets ≥ 75,000/µL and < 100,000/µL
Do not modify dose but recheck CBC in one week. If during subsequent 4 weeks CBCs, ANC remains ≥ 750/µL and platelets remain ≥ 75,000/µL, continue at 100% doses and monitor CBC every 2 - 4 weeks.

b) ANC ≥ 500/µL and < 750/µL and and/or platelets ≥ 50,000/µL and < 75,000/µL

Reduce dose to 50% of original dose until ANC recovers to ≥ 750/µL and platelets recover to ≥ 75,000/µL. Increase dose approximately every two weeks, first to 75% of the original dose and then to full dose, provided ANC remains ≥ 750/µL and platelets remain ≥ 75,000/µL.

c) ANC < 500/µL and/or platelets < 50,000/µL
Discontinue dose 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 week intervals provided ANC remains ≥ 750/µL and platelets remain ≥ 75,000/µL. Consider a marrow evaluation in the face of persistent or prolonged neutropenia.

Prolonged cytopenia is defined as ANC < 750/µL and/or platelets < 75,000/µL after withholding therapy for > 2 weeks. Perform a bone marrow examination after 2 weeks of withholding chemotherapy, if no recovery is apparent. If monocyte count is increasing or viral myelosuppression is clinically suspected, the bone marrow examination may be postponed for 1 - 2 weeks and omitted if ANC and platelets fully recover by the 4th week after therapy is withheld.

If patient develops severe or unexpected myelosuppression, i.e., does not tolerate at least half dose 6-MP, see Section 5.9 on thiopurine pharmacology testing.

For patients with known TPMT or NUDT15 mutations see Section 5.9 for starting doses of 6-MP.

Do not increase doses for persistent high ANC during Consolidation.

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 weekly during Consolidation 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 6-MP monitor labs as above, weekly. Restart at full dose therapy when the transaminases are less than 5x ULN, if bilirubin is normal.

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

5.8.2 PO 6-mercaptopurine (6-MP) Consolidation for B-ALL patients randomized to Arm LR-M.

Do not hold PO 6-MP for uncomplicated myelosuppression. If subsequent course of IV MTX is delayed, HOLD 6-MP until ANC > 500/µL and platelets > 75,000/µL, then restart at 100% dose. Objective is to deliver IV MTX on schedule. If ANC again drops below 500/µL, hold 6-MP until recovery and then restart at 75% dose. Also consider TMP/SMX as possible cause of neutropenia.

For patients with TPMT mutations see Section 5.9 for starting doses of 6-MP.

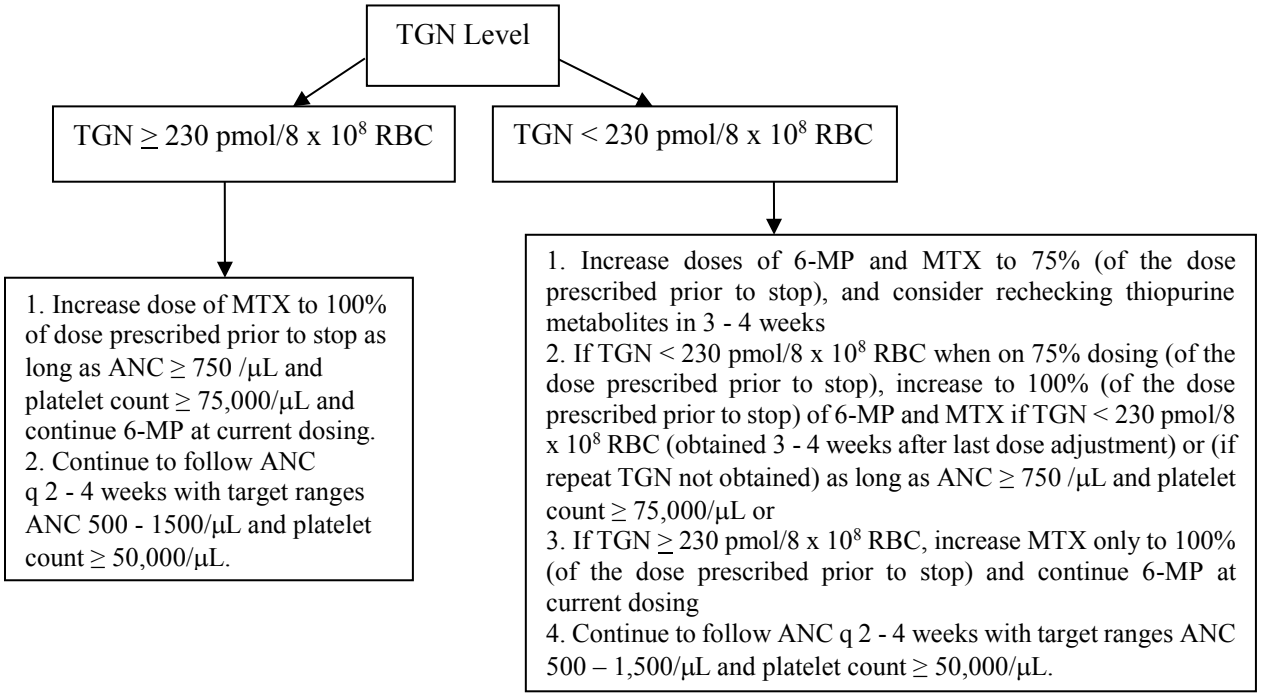
5.9 PO Methotrexate (MTX) and 6-Mercaptopurine (6-MP) – Maintenance for all Arms

In Maintenance, DEX and VCR will be given regardless of blood counts. See Section 5.10 and 5.12 for other adjustments to DEX and VCR.

For patients with TPMT or NUDT15 mutations see below for starting doses of 6-MP.

For low blood counts (without known TPMT or NUDT15 mutations):

- If absolute neutrophil count (ANC) falls below 500/µL or if platelet count falls below 50,000/µL during Maintenance, 6-MP and MTX only will be held until recovery above these levels.
- For the first drop below 500/µL or if platelet count falls below 50,000/µL , resume chemotherapy at the same dose the child was taking prior to the episode of myelosuppression when ANC ≥ 500 /µL and platelet count ≥ 50,000/µL.
- If ANC falls below 500/µL or if platelet count falls below 50,000/µL for a second (or greater) time, discontinue 6-MP and MTX until ANC is ≥ 750/µL and platelets are ≥ 75,000/µL. Consider discontinuing TMP/SMX in favor of an alternative approach to Pneumocystis prophylaxis, as per COG Supportive Care Guidelines (see https://members.childrensoncologygroup.org/prot/reference_materials.asp. When ANC ≥ 750/µL and platelet count ≥ 75 000/µL restart 6-MP and MTX at 50% of the dose prescribed at the time that the medications were stopped.
- Consider obtaining thiopurine metabolites ~ 3 - 4 weeks after restarting the 6-MP and MTX at 50% dose, and following the flow chart below. Consider obtaining repeat thiopurine metabolites ~ 3-4 weeks after the next dose adjustment and using TGN level to guide dosing based on flow chart below. See below if TGN level unknown or unavailable



If TGN level unknown or unavailable

1. Increase doses of 6-MP and MTX to 75% and then 100% of dose prescribed prior to stopping the medications at 2 - 4 week intervals provided ANC remains ≥ 750 /µL and platelets remain > 75,000/µL. May increased both 6-MP and MTX simultaneously. Once at 100% of the dose prescribed prior to stopping, see below for instructions regarding further dose escalation.
2. Continue to follow ANC q 2 - 4 weeks with target ranges ANC 500 – 1,500/µL and platelet count ≥ 50,000/µL

If patient develops severe or unexpected myelosuppression, i.e., doesn't tolerate at least half dose 6-MP, strongly consider evaluation of TPMT and NUDT15 status (see Section below on thiopurine pharmacology testing).

Prolonged cytopenia is defined as ANC < 500/µL and/or platelets < 50,000/µL after withholding therapy for > 2 - 4 weeks. Consider a marrow evaluation in the face of persistent or prolonged neutropenia if no recovery is apparent. If monocyte count is increasing or viral myelosuppression is clinically suspected, the bone marrow examination may be postponed for 1 - 2 weeks and omitted if ANC and platelets fully recover by the 4th week after therapy is withheld.

For persistent ANC ≥ 1,500/µL
No dose escalations are recommended during the first cycle of Maintenance.

- For ANC ≥ 1,500/µL on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s), alternately increase doses of MTX or 6-MP by 25% Always wait at least 4 weeks before making another dose adjustment.
- If both MTX and MP are increased once without a fall in ANC, consider noncompliance as a possibility. Noncompliance can be assessed by obtaining a sample for thiopurine metabolites. A TGN value of ≤ 100 supports non-compliance. Also consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2 - 4 hours later; this value should be ≥ 0.2 micromolar. This will document whether or not poor absorption contributes to lack of response and may facilitate discussions about noncompliance.
- If ANC remains high after intervention for possible noncompliance.
    - For patients who are heterozygous or homozygous deficient for TPMT and have high ANCs as described above, increase MTX alone by 25% and repeat evaluation. Unless noncompliance is suspected, increase MTX preferentially over 6-MP unless TGN is consistently < 230 pmol/8 x 10^8 RBC.
    - For patients who are homozygous wild type for TPMT and have high ANCs as described above, consider increasing the 6-MP dose in 25% increments until ANC is in target. Always wait at least 4 weeks before making another dose adjustment or re-measuring TGN. If ANC remains high, alternate 6-MP dose increases with MTX dose increases.
    - Re consider the possibility of non compliance and/or inappropriate administration of the antimetabolites with food or milk prior to dose escalation.

Thiopurine Pharmacology Testing and Dosage Adjustments:
6-MP and 6-TG are methylated directly by thiopurine methyltransferase (TPMT) to an inactive metabolite. TPMT activity varies tremendously among patients, because of a common inherited genetic defect in TPMT. One in 300 patients is completely deficient (homozygous defective) and 10% of the population are moderately deficient in TPMT activity because they have inherited 1 variant (non-functional) TPMT allele (i.e., heterozygotes).[80-83] 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 6-MP (10 - 30 mg/m^2/day, 3 days per week). About 35% of heterozygotes require a lower dose of 6-MP to avoid dose-limiting myelosuppression.[17]

Recently, germline variants in the gene encoding the nucleoside diphosphate-linked moiety X-type motif 15 (*NUDT15*) were reported in approximately 4% of Hispanic/Native American and nearly 10% of East Asian children with ALL; these polymorphisms are strongly associated with 6-MP intolerance. There are now CLIA certified tests for TPMT genotype and phenotype, for thiopurine metabolites (MMP and TGN measurements), and for *NUDT15* polymorphisms.

Only 3 TPMT SNPs constitute well over 90% of the inactivating mutations in the gene, based on studies in numerous racial and ethnic groups worldwide.[80,84-87] Thus, the genotyping test has a low false negative rate, and may be preferable to TPMT phenotype testing in cases where a history of red cell transfusions would potentially confound assessments of RBC TPMT activity. When the genotyping result is coupled with a phenotyping test for TPMT or with thiopurine metabolite concentrations in erythrocytes, the reliability of the tests will be even greater. Moreover, metabolite levels can provide an index of patient compliance with thiopurine therapy.

Consider TPMT and NUDT15 testing at diagnosis and also consider TPMT genotyping in patients encountering significant myelosuppression during Consolidation therapy.

Recommendations for Thiopurine Monitoring and Dosage Adjustments:
When myelosuppression has led to significant delays in therapy (> 2 weeks) or is disproportionate to the therapy, thiopurine testing could be performed:

- For subjects who have received full dose thiopurine therapy during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict TPMT status and actual thiopurine exposure.
- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status
- TPMT genotyping will be informative in all subjects, if at least 1 mutant allele is identified. If not, and myelosuppression continues, send samples for TPMT activity and/or metabolites since TPMT genotyping will miss 5% - 10% of mutants. NOTE: *Genotyping can be done despite recent transfusions.*

Suggested Dose Adjustments for Patients with Known TPMT Status:

- If the subject is *homozygous deficient* for TPMT or NUDT15, the thiopurine dose should be *reduced to* 10-20 mg/m^2/day 3 days per week. If the SUBJECT is *heterozygous for TPMT and* has experienced significant myelosuppression, the thiopurine dose should be reduced by 30%-50%. It is not yet clear how the dose of thiopurine should be adjusted for patients who are heterozyogous for NUDT15 but such patients should be monitored carefully while on thiopurines. If a patient has two polymorphisms in NUDT15 (i.e. heterozygous for both the R139C and R139H), they should be treated as if they were homozygous deficient. Gradual dose escalations should be attempted as outlined below.

  – Do not increase the dose in response to a high ANC for 4 weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are not often necessary.

- If the subject is homozygous wild-type (high activity) for TPMT or NUDT15, then discontinue TMP/SMX and use pentamidine or dapsone. For modifications of the oral MP and MTX see the beginning of this section (5.9).

In **Consolidation (AR B-ALL, LR B-ALL randomized to Arm LR-C, DS SR B-ALL, B-LLy and DS B-LLy)** consider the following 6-MP dosing based on TPMT status:

- Homozygous wild type: 75 mg/m^2/dose/day. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I.

- Heterozygous: 60 mg/m^2/dose/day. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible.

- Homozygous Deficient: 10 mg/m^2/dose, 3 days/week. A liquid suspension can be prepared. See drug monograph for details.

- Do not increase doses for persistent high ANC during Consolidation

In **Consolidation (B-ALL patients randomized to Arm LR-M)** consider the following 6-MP dosing based on TPMT status:

- Homozygous wild type: 50 mg/m^2/dose/day. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 350 mg/m^2/week as possible See Appendix III.

- Heterozygous: 40 mg/m^2/dose/day. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 280 mg/m^2/week as possible.

- Homozygous Deficient: 10 mg/m^2/dose, 3 days/week. A liquid suspension can be prepared. See drug monograph for details.

- Do not increase doses for persistent high ANC during Consolidation.

In **Maintenance (all Arms)** consider the following 6-MP dosing based on TPMT status:

- Homozygous wild type: 75 mg/m^2/dose/day. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I

- Heterozygous: 60 mg/m^2/dose/day. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible.

- Homozygous Deficient: 10 mg/m^2/dose, 3 days/week. A liquid suspension can be prepared. See drug monograph for details.

- Please note that 65% of heterozygous patients will tolerate full dose 6-MP. During Maintenance (but not Consolidation), adjust as in Section 5.9 if ANC > 1,500/µL persistently. For patients with homozygous deficiency of TPMT, increasing the dose of 6-MP is not recommended.

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 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 6-MP and MTX and monitor labs as above, weekly. Restart at full dose therapy when the transaminases are less than 5x ULN, if bilirubin is normal. If liver dysfunction persists, consider a trial period with MTX but without 6-MP, especially if red cell meTIMP is elevated. Notify Study Chair if both 6-MP and MTX cannot be resumed within 2 weeks. Also consider liver biopsy.

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

5.10 Steroid (Dexamethasone)

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 pro-hemorrhagic 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 (≥ 2.0x ULN).

Osteonecrosis (ON): Do not modify corticosteroid therapy for osteonecrosis (also referred to as avascular necrosis) during Induction or Delayed Intensification. Omit Maintenance steroid for osteonecrosis Grade 2 or greater. Consider resuming Maintenance steroid if joint symptoms have resolved and if MRI findings have significantly improved or normalized.

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

Inability to use oral doses:
For dexamethasone, substitute the IV preparation mg for mg.

Severe infection: Do not hold or discontinue steroids during Induction without contacting the study coordinator. Later in therapy, one may consider holding steroid until patient achieves cardiovascular stability, except for "stress doses."

Severe psychosis: steroid dose may be reduced by 50%.

5.11 PO 6-Thioguanine (6-TG) - Delayed Intensification:

Oral 6-TG will be held for suspected or proven serious infection.
In Delayed Intensification: consider the following 6-TG dosing based on TPMT status:

- Homozygous wild type: 60 mg/m^2/dose/day, etc
- Heterozygous: 50 mg/m^2/dose/day, etc
- Homozygous Deficient: 10 mg/m^2/dose, 3 days/week

For severe and/or unexpected myelosuppression, evaluate for TPMT activity as described in Section 5.9

5.12 **Vincristine**

PLEASE USE "BALIS" SCALE FOR GRADING NEUROPATHY (See text box below)

Severe Neuropathic Pain (Grade 3 or greater):
Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. NOTE: neuropathic pain can be not only severe but difficult to treat. However, because vincristine is an important component of curative therapy and the majority of neuropathies are ultimately reversible, vincristine therapy may be given at full dose at investigator discretion. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out Charcot Marie Tooth Disease (CMT), Type 1A or Hereditary neuropathy with liability to pressure palsies. Drugs such as gabapentin may be of value.

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

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

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

Hyperbilirubinemia[88,89]

Direct Bili	Dose adjustment
< 3.1 mg/dL	None (maximum dose: 2 mg),
3.1- 5.0 mg/dL	50% of calculated dose (maximum dose: 1 mg),
5.1-6.0 mg/dL	25% of calculated dose (maximum dose: 0.5 mg),
> 6.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

Constipation or ileus (> Grade 3) or 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

Motor neuropathy:

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

Sensory neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

5.13 Drug Interactions

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.[90] Neither Gabapentin nor Levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsant. Azole antifungals (listed in the table below) and the macrolide group of antibiotics (listed in the table below) may have potent inhibitory effects on drug-metabolizing enzymes. Patients receiving some antileukemic drugs (e.g. vincristine and anthracyclines) may experience excess toxicity when these agents are given concomitantly; alternate antifungal and antibacterial therapy should be used when possible (see 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*, posaconazole, voriconazole, ketoconazole	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine, anthracyclines, steroids
Macrolide Antibiotics erythromycin, clarithromycin, azithromycin, roxithromycin, telithromycin	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine, anthracyclines, etoposide, steroids

* Itraconazole should NOT be used in patients who are receiving vincristine due to a serious drug-drug interaction leading to severe neurotoxicity.[83, 84]

For a more complete list of CYP 3A 4/5 Inhibitors and Inducers, go to: http://medicine.iupui.edu/flockhart/

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

Possible drug interactions with intermediate dose methotrexate:
When IT therapy and intermediate 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 non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim/sulfamethoxazole (TMP/SMX), penicillins, probenecid, IV contrast media, proton pump inhibitors, phenytoin and fosphenytoin on the days of intermediate dose methotrexate infusion and for at least 72 hours after the start of the intermediate 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

See the consent document for toxicities. All other information is available on the COG website in the manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group" at: https://www.cogmembers.org/_files/disc/Pharmacy/CommercialAgentsMonographs.pdf under **Standard Sections for Protocols.** Also see drug package inserts for added information on toxicities.

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).

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

7.1a Required and Optional Clinical, Laboratory and Disease Evaluations – AR B-ALL and LR B-ALL Randomized to Arm LR-C

		ONLY APPLIES TO PATIENTS ENROLLED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET				
Studies	**Induction**	**Consolidation**	**IM I**	**DI**	**IM II**	**Maintenance**
REQUIRED						
Hx/PE/Wt /Ht[1]	Weekly	Start of Phase	Prior to each IV MTX dose	Days 1, 8, 15, 29	Prior to each IV MTX dose	Every 4 weeks
CBC/diff/platelets	Weekly	Day 1	Prior to each IV MTX dose	Days 1, 8, 15, 29, 36	Prior to each IV MTX dose	Every 4 weeks
Bone Marrow	Baseline & 29[2]					
Peripheral Blood	Days 8[3], 29[3]					
CSF cell count and cytospin	With each IT	With each IT	With each IT	With each IT	With each IT	With each IT
Bilirubin, Albumin[4], ALT and Creatinine	Baseline	Start of Phase	Prior to each IV MTX dose	Days 1, 29	Prior to each IV MTX dose	Day 1 of each 12 week cycle
Varicella titer	Baseline					
Echocardiogram				Prior to first doxorubicin dose[5]		
OPTIONAL						
TPMT and NUDT15 genotype	During Induction					As clinically indicated[6]
Thiopurine metabolites[7]						As clinically indicated[7]
Patient Leukemia Experience Study surveys[8,^]		After Day 15 but prior to start of IM I[^]				Day 29[9,^]
Leukemia Physical Functioning Study evaluations[10,^]		After Day 15 but prior to start of IM I[^]				Day 29[11,^]

[1] The measurement of height (Ht.) for the calculation of BSA is only required at the start of each treatment course/cycle.

[2]Send Day 29 BM to both the ALL Molecular Lab and a COG-Approved ALL Flow Cytometry Lab (see AALL08B1 or APEC14B1 (if open for the classification of newly diagnosed ALL patients) for shipping requirements and addresses).

[3] Send Day 8 PB sample to a COG-Approved ALL Flow Cytometry Lab for MRD and Day 29 PB sample to ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 or APEC14B1 (if open for the classification of newly diagnosed ALL patients) for shipping requirements). **Day 8 PB sample must be collected prior to Day 8 IV/IT chemotherapy.**

NOTE: IF DAY 8 PB AND 29 BM MRD SAMPLES ARE NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

[4] Albumin is collected only during Induction.

[5]Patients with a normal echocardiogram earlier in treatment **do not** need a repeat study.

[6]For AR B-ALL patients in whom TPMT or NUDT15 genotyping was not previously performed (see Section 5.9).

[7] Optional. RBC TGN (or 6-TGN level) & RBC Methyl MP (or 6-MMPN level). Recommended only for AR B-ALL patients during any Maintenance cycle in which 6-MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.9).

[8] Only for AR B-ALL patients already enrolled on Patient Leukemia Experience Study; see Section 15.0 for details of evaluation schedule

[9] Evaluations to be completed on Day 29 (or within 1 month afterwards) of Cycles 1, 4, 7 and end of therapy for boys and Cycles 1, 4, and end of therapy for girls. See Section 15.0 for details of evaluation schedule.

[10] Only for AR B-ALL patients already enrolled on Leukemia Physical Functioning Study (selected institutions-available on the COG AALL0932 protocol webpage); See Section 16.0 for details.

[11] Evaluations to be completed on Day 29 (or within 1 month afterwards) of Cycles 1, 7 and also 1 year post-end of therapy ; evaluations for girls are due on Day 29 (or within 1 month afterwards) of Cycle 1, end of therapy and 1 year post therapy. See Section 16.0 for details.

[^] **The PLES and LPFS have met accrual goals and are closed to new patient enrollment. However, institutions are required to continue data collection at remaining evaluation time points for patients already enrolled.**

7.1b Required and Optional Clinical, Laboratory and Disease Evaluations – LR B-ALL Randomized to Arm LR-M

		ONLY APPLIES TO PATIENTS ENROLLED BEFORE ACCRUAL GOALS FOR AR PATIENTS HAVE BEEN MET	
Studies	**Induction**	**Consolidation**	**Maintenance**
REQUIRED			
Hx/PE/Wt/Ht[1]	Weekly	Days 1, 15, 22, 78 & 85 AND Prior to each IV MTX dose (Days 8, 29, 50, 71, 92 & 113)	Every 4 weeks
CBC/diff/platelets	Weekly	Day 1 AND Prior to each IV MTX dose	Every 4 weeks
Bone Marrow	Baseline, 29[2]		
Peripheral Blood	Days 8[3], 29[3]		
CSF cell count and cytospin	With each IT	With each IT	With each IT
Bilirubin, Albumin[4], ALT and Creatinine	Baseline	Prior to each IV MTX dose	Day 1 of each 16 week cycle
Varicella titer	Baseline		
Serum Creatinine & MTX levels[5]		After each IV MTX dose	
OPTIONAL			
TPMT and NUDT15 genotype	During Induction		As clinically indicated[6]
Thiopurine metabolites[7]			As clinically indicated[7]

[1] The measurement of height (Ht.) for the calculation of BSA is only required at the start of each treatment course/cycle.

[2] Send Day 29 BM to both the ALL Molecular Lab and a COG-Approved Flow Cytometry Lab (see AALL08B1 or APEC14B1 (if open for the classification of ALL patients) for shipping requirements and addresses).

NOTE: IF DAY 8 PB AND 29 BM MRD SAMPLES ARE NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

[3] Send Day 8 PB sample to a COG-Approved ALL Flow Cytometry Lab for MRD and Day 29 PB sample to ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 or APEC14B1 (if open for the classification of newly diagnosed ALL patients) for shipping requirements). **Day 8 PB sample must be collected prior to Day 8 IV/IT chemotherapy.**

[4] Albumin is collected only during Induction.

[5]Monitor levels at the end of the MTX infusion (hour 24), 36 & 42 (only if hour 24 is high) and 48 hours after beginning of the infusion, and every 12-24 hours until the MTX level falls below 0.2µM. See section 5.7.2 for details.

[5] For LR B-ALL patients in whom TPMT or NUDT15 genotyping was not previously performed (see Section 5.9).

[6] Optional. RBC TGN (or 6-TGN level) & RBC Methyl MP (or 6-MMPN level). Recommended only for LR B-ALL patients during any Maintenance cycle in which 6-MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.9).

7.1c Required and Optional Clinical, Laboratory and Disease Evaluations – DS SR B-ALL

Studies	Induction	Consolidation	IM I	DI	IM II	Maintenance
REQUIRED						
Hx/PE/Wt/Ht[1]	Weekly	Start of Phase	Prior to each IV MTX dose	Days 1, 8, 15, 29	Prior to each IV MTX dose	Every 4 weeks
CBC/diff/platelets	Weekly	Day 1	Prior to each IV MTX dose	Days 1, 8, 15, 29, 36	Prior to each IV MTX dose	Every 4 weeks
Bone Marrow	Baseline & Day 29[2]					
Peripheral Blood	Day 29[3]					
CSF cell count and cytospin	With each IT	With each IT	With each IT	With each IT	With each IT	With each IT
Bilirubin, Albumin[4], ALT and Creatinine	Baseline	Start of Phase	Prior to each IV MTX dose	Days 1, 29	Prior to each IV MTX dose	Day 1 of each 12 week cycle
Varicella titer	Baseline					
IgG	Baseline	Start of Phase	Start of phase	Start of phase	Start of phase	Day 1 of each 12 week cycle
Echocardiogram				Prior to first doxorubicin dose[5]		
OPTIONAL						
TPMT and NUDT15 genotype	During Induction					As clinically indicated[6]
Thiopurine metabolites[7]						As clinically indicated[7]

[1] The measurement of height (Ht.) for the calculation of BSA is only required at the start of each treatment course/cycle.

[2] Send Day 29 BM to both the ALL Molecular Lab and a COG-Approved ALL Flow Cytometry Lab (see AALL08B1 or APEC14B1 (if open for the classification of ALL patients) for shipping requirements and addresses).

NOTE: IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

[3] Send Day 29 PB sample to ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 or APEC14B1 (if open for the classification of newly diagnosed ALL patients) for shipping requirements).

[4] Albumin is collected only during Induction.

[5] Patients with a normal echocardiogram earlier in treatment **do not** need a repeat study.

[6] For DS SR B-ALL patients in whom TPMT or NUDT15 genotyping was not previously performed (see Section 5.9).

[7] Optional. RBC TGN (or 6-TGN level) & RBC Methyl MP (or 6-MMPN level). Recommended only for DS SR B-ALL patients during any Maintenance cycle in which 6-MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.9).

7.1d Required and Optional Clinical, Laboratory and Disease Evaluations – B-LLy and DS-B-LLy

Studies	Induction	Consolidation	IM I	DI	IM II	Maintenance
REQUIRED						
Hx/PE/Wt /Ht[1]	Weekly	Start of Phase	Prior to each IV MTX dose	Days 1, 8, 15, 29	Prior to each IV MTX dose	Every 4 weeks
Pregnancy test for females of childbearing potential	Baseline[13]					
CBC/diff/platelets	Weekly	Day 1	Prior to each IV MTX dose	Days 1, 8, 15, 29, 36	Prior to each IV MTX dose	Every 4 weeks
Bone Marrow Cytomorphology	Baseline					
CSF cell count and cytospin	With each IT	With each IT	With each IT	With each IT	With each IT	With each IT
Bilirubin, Albumin[2], ALT, and Creatinine	Baseline	Start of Phase	Prior to each IV MTX dose	Days 1, 29	Prior to each IV MTX dose	Day 1 of each 12 week cycle
Varicella titer	Baseline					
IgG [3]	Baseline	Start of Phase	Start of phase	Start of phase	Start of phase	Day 1 of each 12 week cycle
Echocardiogram				Prior to first doxorubicin dose[4]		
CT (neck, chest, abdomen and pelvis) [5]	Baseline & End of Induction	End of course				Completion of Therapy
Chest X-ray[6]	Baseline & End of Induction	End of course				Completion of Therapy
Bone scan [7]	Baseline & End of Induction	End of course				Completion of Therapy
Diagnostic Biopsy/Cytology	Baseline					
OPTIONAL						
PET scan	Baseline & End of Induction[7]	End of course[8]				
TPMT and NUDT15 genotype	During Induction					As clinically indicated[9]
Thiopurine metabolites[10]						As clinically indicated[10]
Optional Biology Banking[11]	Baseline					
Genetic variation studies (Peripheral Blood) [11]	Day 29[12]					

[1] The measurement of height (Ht.) for the calculation of BSA is only required at the start of each treatment course/cycle.
[2] Albumin is collected only during Induction.
[3] For Down syndrome patients only
[4] Patients with a normal echocardiogram earlier in treatment **do not** need a repeat study.
[5] Repeat all CTs positive at baseline at the end of Induction. For those positive at the end of Induction, repeat at the end of Consolidation.
[6] A chest X-ray is not required if CT chest was performed.
[7] A bone scan at diagnosis is only required in patients with bone symptoms who do not have a PET scan; follow-up scans are only required if the initial scan was positive
[8] A PET scan is highly recommended but not required at diagnosis, at the end of Induction and if there are residual masses at the end of Consolidation.
[9] For all B-LLy patients in whom TPMT or NUDT15 genotyping was not previously performed (see Section 5.9).
[10] Optional. RBC TGN (or 6-TGN level) & RBC Methyl MP (or 6-MMPN level). Recommended only for DS B-LLy patients during any Maintenance cycle in which 6-MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.9).
[11] See Section 14.0 for guidelines on sample handling and shipping.
[12] For patients who consent, send Day 29 PB sample to ALL Molecular Reference Lab for studies of genetic variation (see Section 14.0 for shipping requirements).
[13] Only for patients of reproductive age.

7.2 Studies Suggested to be Obtained After Stopping Therapy (B-ALL Patients)

Note: Refer to COG's Long-term Follow-Up Guidelines for monitoring of long-term complications of therapy, available at: http://www.survivorshipguidelines.org

1st year	PE, CBC/diff/plts q 4-8 weeks, ALT q 2 months until normal BMA, CSF, as clinically indicated*
	Note: for AR patients enrolled on ancillary study(ies); see Sections 15.0 and 16.0 for details of off therapy evaluation schedule.
2nd year	PE, CBC/diff/ platelets q 2 months
3rd year	PE, CBC/diff/ platelets q 3 months
4th year	PE, CBC/diff/ platelets q 6 months
5th year	PE, CBC/diff/ platelets q 6-12 months

***** Obtain at any point after the end of therapy when it is clinically indicated.

7.3 Studies Suggested to be Obtained After Stopping Therapy (B-LLy Patients)

Note: Refer to COG's Long-term Follow-Up Guidelines for monitoring of long-term complications of therapy, available at: http://www. survivorshipguidelines.org

1st year	PE, CBC/diff/platelets q 3 months CT of primary site, BMA, CSF, as clinically indicated*
2nd year	PE, CBC/diff/ platelets q 3 months CT of primary site, as clinically indicated*
3rd year	PE, CBC/diff/ platelets q 4 months CT of primary site, as clinically indicated*
4th year	PE, CBC/diff/ platelets q 6 months CT of primary site, as clinically indicated*
5th year	PE, CBC/diff/ platelets q 12 months

***** Obtain at any point after the end of therapy when it is clinically indicated.

7.4 At Relapse

B-ALL patients who relapse and have consented to cell banking when they consented to AALL08B1 or APEC14B1 (*if open for the classification of newly diagnosed ALL patients*), should have samples of bone marrow sent to the Molecular Reference Laboratory for cell banking as described in AALL08B1 or APEC14B1

7.5 Sample and Shipping Information

For a list of COG-Approved Flow Cytometry Labs, see :
https://members.childrensoncologygroup.org/_files/admin/mrdflowlabs.pdf

Molecular Laboratory

Julie Gastier-Foster, PhD
COG ALL Reference Laboratory
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215
Phone : (614) 722-2866
Fax : (614) 722-2887
Email : MGLab@nationwidechildrens.org

8.0 SUPPORTIVE CARE GUIDELINES

8.1 General Guidelines

Aggressive supportive care improves outcome. The following guidelines are intended to give general direction for optimal patient care and to encourage uniformity in the treatment of this study population. Notify Study Chair of any unexpected or unusually severe complications. Please also see the COG Supportive Care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp

See Section 8.3 for DS patients.

8.1.1 Blood Components

Blood products should be irradiated following current FDA guidelines found at:
http://www.fda.gov/OHRMS/DOCKETS/98fr/981218g2.pdf

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 (RBC)

Transfusion with RBC is indicated to correct severe or symptomatic anemia or acute blood loss. In the setting of extreme hyperleukocytosis investigators should be mindful that peripheral red blood cells (PRBC) may contribute to hyperviscosity.

Platelets

Transfusion with platelets is indicated to correct bleeding manifestations and may be indicated for severe thrombocytopenia without bleeding particularly prior to an invasive procedure.

8.1.2 Infection Prophylaxis

Pneumocystis jiroveci

All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 5 mg/kg/day divided bid 2 - 3 sequential days per week. For patients allergic to or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone (1 - 2 mg/kg/day, maximum dose 100 mg/day), aerosolized pentamidine (300 mg/q month ≥ 5 years of age), or atovaquone (30 mg/kg/day if < 3 months or > 2 years, 45 mg/kg/day if between 3 months & 2 years) may be considered. For children in whom TMP/SMX, dapsone, atovaquone, and inhaled pentamidine cannot be administered, IV pentamidine (4 mg/kg/dose IV every 2 to 4 weeks) should be given. (REF: Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR 2000; 49(No. RR-10):1-125. Available at http://www.cdc.gov/mmwr/PDF/rr/rr4910.pdf. Accessed December 1, 2007.)

Varicella Vaccine

May be given to the siblings of patients in remission and stable at the physician's discretion. Varicella vaccination is not recommended for ALL patients during therapy.

Gamma globulin

If clinically indicated, IgG levels may be monitored throughout treatment. If the IgG level falls below age determined normal levels, IVIG at 400 mg/kg may be administered at the discretion of the investigator. Note of IVIG administration should be recorded on data form.

Antifungals

Azole antifungal agents (i.e. fluconazole, itraconazole, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity. Caution is advised if azole antifungals are used.

8.1.3 Treatment of Established or Presumed Infections

Fever with Neutropenia

For patients with ANC < 500/µL or expected to fall to this level within the next 48 hours and an oral-equivalent temperature ≥ 38.3°C once or between 38.0°C and 38.3°C twice within 12 hours, empiric broad spectrum antibiotics should be instituted after obtaining appropriate cultures. Patients who present with severe sepsis should have empiric antibiotic coverage widened to include resistant Gram-negative, Gram positive, and anaerobic bacteria.

The risk of bacteremia and infectious morality is higher during Induction and during profound neutropenia. The specific choice of antibiotics to be used in empiric treatment of febrile neutropenia is dependent on each institution's experience regarding the type of infecting organisms, and their antibiotic sensitivity patterns. For prolonged fever and neutropenia (≥ 96 hours), empiric antifungal therapy with either caspofungin or liposomal amphotericin B should be given during periods of anticipated prolonged neutropenia including induction.

Also, please see the COG Fever and Neutropenia Guidelines at:
https://childrensoncologygroup.org/downloads/COG_SC_FN_Guideline_Document.pdf

Primary Varicella Infection (Chickenpox)

Patients should be treated promptly with acyclovir 1,500 mg/m²/day intravenously divided q 8 hours, and monitored closely for the development of invasive systemic disease.

Empiric Management of Pulmonary Infiltrates

Pulmonary infiltrates should be evaluated in the context of the patient's clinical and laboratory profile as well as institutional infection patterns. If the patient is not neutropenic, and the pulmonary lesions on CT scan are not particularly suggestive of a fungal infection (Aspergillus, mucor), consider using broad spectrum antibiotics. If the patient develops progressively worsening clinical or laboratory features, or if, the pulmonary lesions on CT scan are suggestive of a fungal infection (Aspergillus, mucor), then more aggressive diagnostic measures should be undertaken. Pulmonary infiltrates may be evaluated with bronchoscopy and biopsy, lavage or open lung biopsy. If a procedure cannot be tolerated, and/or if there is high clinical suspicion consider beginning empiric treatment with amphotericin B given the high likelihood of fungal disease. It is advisable to seek an infectious disease consult under these circumstances. Empiric coverage may include treatment for gram-negative and positive bacteria, Legionella (erythromycin), Pneumocystis (TMP/SMX), and fungi (amphotericin) pending culture results. If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis and brain are indicated. Surgical excision of pulmonary lesions should be considered at the discretion of the treating physician. Treatment of fungal infections with amphotericin B and/or other antifungal agents will be at the discretion of the treating physician. **Azole antifungal agents (i.e. fluconazole, itraconazole, voriconazole) given concurrently with vincristine may INCREASE the risk of neurotoxicity. Caution is advised if azole antifungals are used.**

Management of Mucositis/Perirectal Cellulitis

Mucositis should be managed with IV hydration and hyperalimentation if indicated, effective analgesia, broad-spectrum gram-positive and gram-negative antibiotic therapy and empiric antiviral and antifungal therapy as indicated. Management of perirectal cellulitis should include broad-spectrum antibiotic therapy with dual gram-negative coverage as well as anaerobic coverage (i.e. ceftazidime + aminoglycoside +

metronidazole; or piperacillin-tazobactam + aminoglycoside), Sitz baths, a strong barrier technique and effective analgesia.

8.1.4 Prevention and Management of Chemotherapy induced Nausea and Vomiting (CINV)
Please refer to the COG Endorsed guidelines on prevention and management of CINV at: https://childrensoncologygroup.org/downloads/COG_SC_CINV_Guideline_Document.pdf.

The routine use of steroids including dexamethasone, is discouraged but may be appropriate in select patients with demonstrated intolerance to higher-dose chemotherapeutic agents.

8.1.5 Use of Filgrastim
The routine use of filgrastim is not generally recommended, but may be used at the discretion of the investigator in situations of serious infection with neutropenia.

8.1.6 Osteonecrosis (ON)
Osteonecrosis (also referred to as avascular necrosis) may develop during or following therapy and often involves multiple joints over time. ON is not limited to weight bearing joints; common sites include hip, knee, ankle, heel, shoulder and elbow. Symptoms and exam findings may include joint pain, joint stiffness, limited range of motion (e.g. pain with internal rotation of the hip), limited mobility or ambulation, and/or gait abnormalities. Diagnostic imaging is indicated in any patient with suggestive findings. MRI is superior in sensitivity and specificity to other modalities, especially with early bone changes. Patients with negative studies, but who have persisting, progressive, or recurrent symptoms, should be re-imaged. For modifications of ALL therapy, see Section 5.10.

8.1.7 GI Protection
While patients are on steroid therapy, consider using an H2 blocker.

8.2 Guidelines for Induction

8.2.1 Acute Tumor Lysis Syndrome
Patients with ALL at high risk of tumor lysis should be assessed rapidly for evidence of symptomatic hyperleukocytosis, tumor lysis syndrome, and coagulopathy. Suggested initial studies, obtained prior to initiating antileukemia therapy, may include a complete blood count (CBC), prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes, including creatinine, BUN, uric acid, phosphorus, and calcium. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated.

The risk for serious acute tumor lysis syndrome (TLS) is usually restricted to the first 72 hours after initiation of therapy; however, it may spontaneously occur prior to treatment. To manage the metabolic derangements caused by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, the following steps should be initiated:

1. Begin allopurinol at a dose of 300 mg/m²/day or 10 mg/kg/day (maximum 800 mg/day) in 2 - 3 divided doses and continue until peripheral blasts and extramedullary disease are reduced. In some situations it may be also be appropriate to use rasburicase.
2. Hydrate at 2,400-3,000 mL/m²/day to maintain urine output > 100 mL/m²/hour until peripheral blasts and extramedullary disease are reduced. Potassium should not be added to the hydration fluids.
3. Urine alkalinization is NOT necessary for TLS prophylaxis. There is paucity of evidence demonstrating benefit of urine alkalinization and it can potentially lead to calcium phosphate precipitation and/or metabolic acidosis.

If the patient has oliguria or severe renal dysfunction, consider the use of rasburicase at 0.1 to 0.2 mg/kg/dose (or as per institutional guidelines) and obtaining a nephrology consult. In patients with a prior history of

glucose-6-phosphate dehydrogenase (G-6PD) deficiency, rasburicase is contraindicated and allopurinol should be utilized instead of rasburicase.

Refer also to the discussion of TLS in the Supportive Care Manual (Supportive Care of Children with Cancer, ed A Altman, 3rd edition, 2004).

8.2.2 Diagnostic Lumbar Puncture

As there are data that suggesting that traumatic diagnostic lumbar punctures may have an adverse effect on prognosis, consider interventions to minimize the chances of a traumatic diagnostic lumbar puncture (LP).[91] These interventions may include:

a) Correcting any coagulopathy or thrombocytopenia (goal: platelets > 100 000/μL) present prior to the diagnostic LP
b) Performing the diagnostic LP while the patient is in a controlled environment such as under deep sedation.[91]
c) Administering intrathecal cytarabine at the time of the diagnostic lumbar puncture.
d) Having the diagnostic lumbar puncture performed by an experienced provider to minimize unintentional trauma.

8.2.3 Induction – Infectious Complications

Since the induction phase is associated with a higher rate of toxicity, investigators are cautioned to pay close attention to a number of factors during the early phases of treatment. Patients may experience profound myelosuppression and immune suppression during this time. Since steroids may mask fever, as well as other components of the inflammatory response sepsis during Induction, the warning signs of septic shock may be associated with very mild and subtle symptoms. Caregivers must also be made aware that patients may experience very rapid clinical deterioration. This suggests the need for a supportive care network that can recognize and respond to sudden changes in a patient's condition. In addition it should be noted that several serious toxic events have had an intestinal component. Patients with subtle GI symptoms should be monitored very closely.

8.3 **Patients with Down syndrome**

Patients with DS B-ALL and DS B-LLy have a significantly increased risk of morbidity and treatment-related mortality in most published series.[37] Therefore, they require diligent and conservative supportive care. Infectious complications during times of neutropenia are of greatest concern. The pattern of treatment-related mortality among HR-DS-ALL patients enrolled on AALL1131 as of May 2015 suggests there may be an increased risk associated with age greater than or equal to 15 years and/or obesity during the following treatment phases: Induction, Consolidation, and Delayed Intensification. Infections in children with Down syndrome may be sudden in onset and progress rapidly mandating close surveillance and aggressive intervention or treatment..

It is strongly recommended that children with Down syndrome be *monitored in the hospital* during Induction and Delayed Intensification until they show signs of bone marrow recovery (and, is afebrile, and clinically stable). If a patient experiences profound myelosuppression at any other time, there should also be a very low threshold for hospitalization and inpatient management until there is evidence of bone marrow recovery. *Antibiotic prophylaxis* against Gram-positive and Gram-negative organisms (e.g. Levofloxacin[92,93]) may be considered during periods of severe myelosuppression until patients meet criteria for discharge with a switch to broad-spectrum intravenous antibiotics per institutional guidelines if a patient develops febrile neutropenia while receiving prophylactic antibiotics. *Antifungal prophylaxis* may also be considered during periods of myelosuppression. Options include an echinocandin such as caspofungin or micafungin, or an azole. Investigators should be cautious however as a**zole antifungal agents (i.e.,**

fluconazole, itraconazole, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity.

IgG levels should be monitored monthly and strong consideration given to IVIG therapy for levels less than 500 mg/dL. IgG levels and route of IVIG administration should be recorded on study CRF.

Children with DS B-ALL and DS B-LLy may not develop fever in response to infection, even with sepsis, particularly when they are receiving steroids. Therefore extra vigilance is needed, with a lower threshold for drawing cultures and starting antibiotics, even for subtle changes in clinical status. Aggressively manage episodes of fever (≥ 100.5ºF/38.05°C) during Induction and Delayed Intensification or when the patient is neutropenic with an ANC ≤ 1,000/μL. The risk of life threatening infection is high so these patients should be hospitalized with immediate institution of broad spectrum IV antibiotics adjusted appropriately for local patterns of antibiotic resistance. Adequate coverage for gram negative and positive organisms including viridans streptococci is recommended. Broad spectrum antibiotics, once started, should continue until evidence of bone marrow recovery. In the absence of response after 3 – 5 days, institution of antifungal therapy should be strongly considered. *Stress-dose steroids and/or filgrastim* should be considered in DS B-ALL and DS B-LLy patients with fever and neutropenia who are very ill or not responding appropriately to antibiotic therapy.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy for B-ALL and B-LLy Patients

a) Identification of Very High Risk B-ALL features at the end of Induction. [1]
b) Recurrent leukemia following complete remission. (B-ALL only)
c) Identification of High Risk B-ALL features at the end of Induction. [2]
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Identified as Philadelphia chromosome-positive (*BCR-ABL1*). [3]
f) Completion of planned therapy.
g) Down syndrome patients identified as Induction failure (M3 at Day 29) (B-ALL only)
h) Physician determines it is in patient's best interest.
i) Development of a second malignancy.
j) Adverse Event/Side Effects/Complications
k) Incomplete Induction data for risk stratification. (B-ALL only)
l) Down syndrome patient identified to be Down syndrome high risk B-ALL.[4]
m) Inevaluable
n) Progressive disease at any time point prior to the end of Consolidation (B-LLy only)
o) Failure to achieve CR at the end of Consolidation (B-LLy only).
p) Relapsed biopsy proven lymphoma following CR (B-LLy only)
q) Identification of Average Risk B-ALL features at the end of Induction.[5]
r) Identification of Low Risk B-ALL features at the end of Induction.[5]

[1] M3 marrow at end of Induction; or KMT2A (MLL) gene rearrangement; or hypodiploid; or iAMP21, or no favorable cytogenetics with Day 29 MRD ≥ 0.01%.
[2] Favorable cytogenetics with Day 29 MRD ≥ 0.01%; or no favorable cytogenetics with Day 8 MRD ≥1% and Day 29 MRD < 0.01% MRD.
[3] B-ALL Ph+ patients are eligible for enrollment on AALL1122 or successor study by Day 15 of Induction.
[4] Eligible for post-Induction therapy on the High Risk study.
[5] Only applies to patients enrolled after accrual goals for AR patients have been met.

B-ALL and B-LLy 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.

9.2 Off Study Criteria (B-ALL and B-LLy Patients)

a) Death.
b) Lost to follow-up.
c) Enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence) with the exception of COG AALL1421, a Phase 2 study of IV pegcristantaspase, a pegylated *Erwinia* asparaginase, as a replacement for pegaspargase in patients with pegaspargase hypersensitivity.
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of study entry.

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Design

Primary Endpoint

A primary endpoint for the Average Risk (AR) patients will be the improvement in 5-year disease free survival (DFS) from 93% to 96% based on the MTX randomization. The second endpoint is to determine if the 5-year DFS is adversely affected by the reduced pulses in Maintenance (every 4 weeks vs. every 12 weeks). DFS for the AR patients is defined as the time from randomization at the end of IM II to first event (relapse, second malignancy, remission death) or date of last contact. Another endpoint is to determine if less intensive therapy will maintain a 5-year DFS $\geq$ 95% for the Low Risk (LR) patients, where patients will be randomized 1:1 to one of two low intensity regimens (Arm LR-C vs. Arm LR-M). The primary objective is not to compare outcomes on the 2 arms but to determine if outcomes on each arm are $\geq$ 95%. The 5-year DFS for the DS patients will also be estimated on modified therapy. For the LR and DS patients, DFS is defined as the time from end of Induction to first event (relapse, second malignancy, remission death) or date of last contact.

Secondary Endpoint – See Correlative Studies in Sections 15.0 and 16.0.

10.2 Patient Accrual and Expected Duration of Trial

Total Expected Accrual: 5,872 over 4.9 years. Of 1,200 NCI SR patients, a total of 1,186 patients (less 12 CNS3 patients and 2 patients with testicular disease at diagnosis) will be enrolled on this study annually. Patients with CNS3 or testicular disease will be eligible for COG AALL1131. About 32 of these will be patients with DS. These patients will be assigned to a separate stratum and will receive separate Induction and post-Induction therapy. All other patients will receive standard 3 drug Induction. At the end of Induction, patients identified to be LR (250 patients/year) will be assigned to a separate stratum to receive less intensive post-Induction therapy. They will be randomized 1:1 to two low-intensity therapeutic regimens at the end of Induction. We estimate that 89 NCI SR patients without favorable cytogenetics, will be removed from this study per year at the end of Induction due to Day 8 MRD $\geq$ 1%, with Day 29 MRD < 0.01%. These patients will be eligible to participate in post-Induction therapy assignment/randomization on the HR trial. Patients with favorable cytogenetics who have Day 29 BM MRD $\geq$ 0.01% (70 patients/year) will be removed from this study at the end of Induction and will also be eligible for post induction therapy on the HR study. Patients without favorable cytogenetics that have Day 29 MRD $\geq$ 0.01% (79 patients/year) will be removed from therapy at the end of induction and will be eligible to receive post induction therapy on the VHR study. About 38 patients/year with other high risk features (KMT2A (MLL), hypodiploid, M3 marrow end Induction, iAMP21) will be removed from therapy at the end of Induction and may be eligible for the VHR study. About 12 patients/year will be found to be Ph+ and will be removed from therapy by Day 15 of Induction and may be eligible for AALL1122 or successor COG Ph+ ALL trial. About 5 DS patients will be Day 29 MRD positive and will be eligible to transfer to the HR study. The remaining

616 patients/year will be the AR patients. These patients will be randomized at the end of IM II to 2 questions. The first is a randomization between 20 mg/m^2 and 40 mg/m^2 of weekly oral MTX in Maintenance. The second is a randomization between every 4 weeks and every 12 weeks VCR/DEX pulses in Maintenance. The first question is a therapy intensification question and will look for an improvement in DFS while the second will be a reduction in therapy question looking for non-inferiority in DFS.

Amended Accrual (Amendment #2A):
Assuming an accrual rate of 15 patients/year with Murphy Stages I and II B-Lymphoblastic Lymphoma (B-Lly) would result in a total accrual of about 60 B-Lly patients over the remaining 4 years of accrual of the study. All patients with Murphy Stages I and II B-Lly (without Down syndrome) will be non-randomly assigned to post-Induction therapy similar to patients with AR B-ALL, with a modified Maintenance Arm A (**Arm LLy**), on AALL0932. Down syndrome B-Lly patients will be non-randomly assigned post-induction to DS SR B-ALL with Maintenance "Arm DS".

Amended Accrual (Amendment #3A): The enrollment of this study will be extended until AALL1131 meets accrual goals (anticipated December 2017). All enrolled patients will receive Induction treatment on AALL0932. Once the Average Risk (AR) arm meets accrual goals (i.e. 2,396 randomized evaluable patients), both the AR and LR arms will be closed to accrual and all patients who are classified as AR or LR will come off protocol therapy upon completion of Induction. The Down syndrome (DS) and B-lymphoblastic lymphoma (B-LLy) strata will remain open until the end of the study accrual. Patients who are classified as HR or VHR at end of Induction will continue to be eligible for enrollment on AALL1131.

As of 12/31/2014, the study has accrued a total of 5,269 patients, including 531 evaluable LR, 129 eligible SR-DS and 18 eligible B-LLy patients. With extended accrual to the end of 2017, the total number of patients to be enrolled to the study is estimated to be 9,022 (accrual rate is ~ 1,251/year) and the total number of eligible patients to be enrolled to the SR-DS and B-LLy groups are around 222 (accrual rate is ~ 31/year) and 48 (accrual rate is ~ 10/year), respectively.

In order to accrue the 2,396 patients who complete the Maintenance therapy randomization, the study is projected to enroll approximately 3,195 AR patients to account for those who decline randomization. As of 12/31/2014, a total 2,764 AR patients have been enrolled to the post-Induction therapy. With the estimated accrual rate of 657/year, the AR group is projected to meet accrual goals in August 2015. Given the observed accrual of 125/year for LR patients, the total number of evaluable patients to be enrolled to the LR randomization is approximately 614.

Amended Accrual (Amendment #4): The enrollment of this study will be extended until AALL1131 meets accrual goals (anticipated April 2018). All enrolled patients will receive Induction treatment on AALL0932. The Average Risk (AR) and Low Risk (LR) arms were closed to accrual on 05/29/2015, and since then, all enrolled patients after who are classified as AR or LR will come off protocol therapy upon completion of Induction. The Down syndrome (DS) and B-lymphoblastic lymphoma (B-LLy) strata will remain open until the end of the study accrual. Patients who are classified as HR or VHR at end of Induction will continue to be eligible for enrollment on AALL1131.

As of 03/28/2016, the study has accrued a total of 6,862 patients, including 603 randomized LR, 3125 AR (2365 randomized at the start of Maintenance), 165 eligible SR-DS and 28 eligible B-LLy patients. With extended accrual to the end of April 2018, the total number of patients to be enrolled to the study is estimated to be 9,483 (accrual rate is ~ 1,258/year) and the total number of eligible patients to be enrolled to the SR-DS and B-LLy groups are around 228 (accrual rate is ~ 30/year) and 47 (accrual rate is ~ 9/year), respectively.

10.3 **Statistical Analysis Methods**

Sample size with power justification

The study will be powered to answer the reduction in therapy question among the Average Risk (AR) patients (5 year DFS 93% on every 4 weeks vs. 90% on every 12 weeks reduced pulses). A total of 2,396 patients will give 90% power (alpha = 10%, one-sided), to detect a reduction in 5 year DFS from 93% to 90% (HR = 0.689; 204 events). Accounting for 25% loss to randomization due to various reasons, a total of 2,996 AR patients will be accrued over 4.9 years. A total of 2,396 eligible, evaluable patients will give 93.6% power (alpha = 5%, one-sided) to detect an improvement in 5 year DFS from 93% vs. 96% for the MTX question (HR: 0.5625; 132 events). All patients will be followed for a minimum of 3 years.

If it is found that there is a decrease in DFS due to the reduced pulses, comparison of outcomes between the two MTX regimens will be restricted to the q4 week pulses arms. With half the sample size (N = 1,198) there will be 72.5% power to detect a difference in 5 year DFS from 93% to 96% (alpha = 5%, 66 events) on the two MTX regimens; and 92.9% power to detect an improvement from 93% to 97%. As and when interim monitoring indicates erosion in DFS due to the reduced pulses, that randomization will be closed and accrual to the MTX randomization (with all patients receiving every 4 week pulses) will continue until a total of 1486 patients are accrued on the two MTX (with 4 week steroid pulses) regimens. A total of 1,486 pts would give 80% power to see an improvement in DFS from 93% to 96%.

A Cox proportional hazards model will be used to test for quantitative interaction in this 2x2 factorial design. But the sample sizes will not be large enough to power it to detect interactions of the same magnitude as the main effects size. If there is significant interaction between the 2 factors, the 4 regimens can be compared using an adjusted alpha level.

A total of 1,200 eligible, evaluable LR patients will be accrued over 4.9 years randomized 1:1 to either of the 2 low intensity regimens. The 5 year DFS for these patients will be estimated on the 2 low intensity regimens. The objective is not to compare the 2 regimens with respect to outcomes, but estimate the DFS on each low intensity regimen. With a sample of 600 patients on each regimen, the DFS can be estimated for each regimen with a maximum standard error of 2%. The expected 5 year DFS on each of these regimens is at least 95%. If so, either would be deemed suitable for future use in this patient population. Assuming a baseline 5 year DFS of 95%, there is 83.3% power to detect a difference (95% vs. 98%) using a 2 sided log rank test with alpha = 5%. The sample size is not large enough to design this as an equivalence study.

A total of 130 eligible, evaluable DS patients will be enrolled during this study. The 5 year DFS for these patients will be estimated. A sample of 130 pts will allow the DFS to be estimated with a maximum standard error of 4.4%.

All power calculations are based on the assumption of proportional hazards, and using the log rank test (alpha = 5%) with 5 planned analyses of the data for interim monitoring purposes (MTX question for AR patients). The efficacy stopping boundaries to be used will allocate greater importance to the later analyses. The upper boundaries selected are based on the alpha × $(time)^2$ spending function. The study will also be monitored for futility. The lower boundaries are based on testing the alternative hypothesis at the 0.005 level.[94] 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 DFS event horizon (total events = 132) for the overall randomized group.

At the time of each interim monitoring, we will also monitor for a decrease in DFS due to the reduced pulses. Interim monitoring will be based on the alpha × $(time)^2$ spending function (alpha =10%, one-sided test) and will be conducted at the same time as the interim analyses for the MTX question. If it is found that

there is erosion in outcomes on the reduced pulses arm compared to the 4 week pulses regimen, this randomization will be closed and all patients will be assigned to the 4 week pulses arm.

Interim analysis will also be conducted for each of the 2 low intensity regimens to protect against lower DFS for the LR patients. A 5 year DFS of 95% translates to a hazard rate of 0.0103. Interim analysis will be based on the estimated hazard rate. The αt^2 spending function will be used to maintain an overall one-sided Type I error rate of 10%. Interim analyses will be done at the time of the above analyses.

Amendment #3A: An estimate of 614 eligible, evaluable LR patients will be randomized 1:1 to the 2 low-intensity regimens. The 5 year DFS for these patients will be estimated on the 2 arms. The objective is not to compare the 2 regimens with respect to outcomes, but estimate the DFS on each low-intensity regimen. With a sample of 307 patients on each regimen, the DFS can be estimated for each regimen with a maximum standard error of 2.9%. The expected 5 year DFS on each of these regimens is at least 95%. If so, then either would be deemed suitable for future use in this patient population. Assuming a baseline 5 year DFS of 95%, there is 52.2% power to detect a difference (95% vs. 98%) between the two arms using a 2-sided log rank test with alpha = 5%.

A total of 222 eligible, evaluable DS patients will be enrolled during this study. The 5-year DFS for these patients will be estimated. A sample of 222 patients will allow the DFS to be estimated with a maximum standard error of 3.6%.

Interim analysis will also be conducted for each of the 2 low intensity regimens to protect against lower DFS for the LR patients. A 5-year DFS of 95% translates to a hazard rate of 0.0103. Interim analysis will be based on the estimated hazard rate. The alpha × $(\text{time})^2$ spending function will be used to maintain an overall one-sided Type I error rate of 10%. Interim analyses will be done at the time of the above analyses. There was no reported DFS event for LR patients as of the last reporting cycle of Fall 2014.

All the above primary analyses of DFS comparisons between randomized groups are intent-to-treat analyses. Secondary analyses will include DFS comparisons accounting for the number of patients on each arm who were also enrolled on AALL1421 in order to adjust for any potential impacts on DFS with the use of PEG-Erwinia.

Amendment #4:
The 5 year DFS for LR patients will be estimated on the 2 arms. The objective is not to compare the 2 regimens with respect to outcomes, but estimate the DFS on each low-intensity regimen. With the 603 LR patients randomized to the 2 low-intensity regimens, the DFS can be estimated for each regimen with a maximum standard error of 2.9%. The expected 5 year DFS on each of these regimens is at least 95%. If so, then either arm would be deemed suitable for future use in this patient population. Assuming a baseline 5 year DFS of 95%, there is 51.9% power to detect a difference (95% vs. 98%) between the two arms using a 2-sided log rank test with alpha = 5%.

A total of 228 eligible, evaluable DS patients will be enrolled during this study. The 5-year DFS for these patients will be estimated. A sample of 228 patients will allow the DFS to be estimated with a maximum standard error of 3.3%.

Interim analysis will also be conducted for each of the 2 low intensity regimens to protect against lower DFS for the LR patients. Interim analysis will be based on the Woolson's one-sample logrank test, assuming the survival time for LR patients follows a cure-rate model with exponential distribution assumed during the first 4 years followed by a flat curve. The alpha × $(\text{time})^2$ spending function will be used to maintain an overall one-sided Type I error rate of 10%. Interim analyses will be done at the time of the above analyses. There were 2 reported DFS events for LR patients as of the last reporting cycle of Fall 2015.

All the above primary analyses of DFS comparisons between randomized groups are intent-to-treat analyses. Secondary analyses will include DFS comparisons accounting for the number of patients on each arm who were also enrolled on AALL1421 in order to adjust for any potential impacts on DFS with the use of PEG-Erwinia.

Amended Design (Amendment #2A):
From past studies, almost 100% of B-LLy patients have submitted biospecimens. Study pathologists estimate viable samples for 90% of enrolled patients resulting in a total of 54 B-LLy patients available for analyses. The 5 year EFS for these patients is around 90% from past studies (A5971). The 5 year EFS rate will be estimated for this group of patients. The 95% confidence interval will be computed for the same. We will monitor outcomes for these patients to ensure against significant erosion in EFS rates. Assuming that most events have occurred within 5 years and that the survival curve is relatively flat beyond this time point, the binomial distribution can be used to model the number of events at the 5-year time point. If at least 8 events (induction failures, progressive disease, relapse, second malignancy, or death) occur among the 54 B-LLy patients, it will be concluded that the 5 year EFS is less than 90%. With this design there is a 16.8% chance of erroneously concluding that there is a decrease in EFS when in fact the true 5 year EFS is 90%. The probability is 87.2% of concluding there is a decrease in EFS when the true 5 year EFS is 80%. The 5 year EFS and OS will be estimated separately for the B-LLy patients. Biology data captured for these patients will be summarized. Due to small patient numbers, analyses will be descriptive.

Amendment #3A: The actual accrual rate for B-LLy is about 10 patients per year, which is less than the previously projected rate of 15 per year. With the extended accrual to the end of 2017, the total number of B-LLy patients to be accrued to the study is approximately 48. Study pathologists estimate viable samples for 90% of enrolled patients resulting in a total of 43 B-LLy patients available for analyses. The 5 year EFS for these patients is around 90% from past studies (A5971). The 5-year EFS rate will be estimated for this group of patients. The 95% confidence interval will be computed for the same. We will monitor outcomes for these patients to ensure against significant erosion in EFS rates. Assuming that most events have occurred within 5 years and that the survival curve is relatively flat beyond this time point, the binomial distribution can be used to model the number of events at the 5 years time point. If at least 7 events (induction failures, progressive disease, relapse, second malignancy, or death) occur among the 43 B-LLy patients, it will be concluded that the 5 year EFS is less than 90%. With this design there is a 13.3% chance of erroneously concluding that there is a decrease in EFS when in fact the true 5 year EFS is 90%. The probability is 78.4% of concluding there is a decrease in EFS when the true 5 year EFS is 80%. The 5 year EFS and OS will be estimated separately for the B-LLy patients. Biology data captured for these patients will be summarized. Due to small patient numbers, analyses will be essentially descriptive in nature.

Amendment #4: The current accrual rate for eligible B-LLy is about 9 patients per year, which is less than the previously projected rate of 15 per year. With the extended accrual to the end of April 2018, the total number of eligible B-LLy patients to be accrued to the study is approximately 47. Study pathologists estimate viable samples for 90% of enrolled patients resulting in a total of 42 B-LLy patients available for analyses. The 5 year EFS for these patients is around 90% from past studies (A5971). The 5-year EFS rate will be estimated for this group of patients. The 95% confidence interval will be computed for the same. We will monitor outcomes for these patients to ensure against significant erosion in EFS rates. Assuming that most events have occurred within 5 years and that the survival curve is relatively flat beyond this time point, the binomial distribution can be used to model the number of events at the 5 years time point. If at least 8 events (induction failures, progressive disease, relapse, second malignancy, or death) occur among the 42 B-LLy patients, it will be concluded that the 5 year EFS is less than 90%. With this design there is a 5.4% chance of erroneously concluding that there is a decrease in EFS when in fact the true 5 year EFS is 90%. The probability is 62.2% of concluding there is a decrease in EFS when the true 5 year EFS is 80%. The 5 year EFS and OS will be estimated separately for the B-LLy patients. Biology data captured for these

patients will be summarized. Due to small patient numbers, analyses will be essentially descriptive in nature.

The following specific toxicities identified by the ALL Toxicity Reporting Task Force will be collected on all future COG ALL trials (including this one) in addition to any Grade 4 non-hematologic toxicities for all patients on study (B-ALL and B-LLy):

1. CNS hemorrhage requiring medical intervention (Grade 2 or 3)
2. GI bleed requiring operative or interventional radiology intervention (Grade 3)
3. Pancreatitis requiring medical intervention (Grade 2 or 3)
4. Osteonecrosis interfering with function (Grade 2 or 3)
5 Transient ischemic attacks (All grades)
6. Stroke (All grades)
7. Encephalopathy (Grade 3)
8. Neuropathy; motor or sensory, interfering with ADL (Grade 3)
9. Seizure (Grade 2 or 3)
10. Allergic reaction (Grade 3)
11 Ileus (Grade 3)
12. Mucositis/stomatitis; functional (Grade 3)
13. Bilirubin (Grade 3)
14. Thrombosis (Grade 3)

Additional reporting requirements for AR B-ALL patients:

Detailed dosing data on 6-MP and MTX will be collected during Maintenance, in order to assess the ability to deliver the protocol specific methotrexate dose intensity. On the previous Standard Risk ALL trial (CCG-1991), some dosing data was collected. That data suggests that approximately 50% of patients have dose reductions during each Maintenance cycle. There is concern that patients assigned to the higher dose of MTX (40 mg/m^2) may have lower doses of mercaptopurine administered and/or may have medications held more frequently than patients assigned to the lower dose of MTX (20 mg/m^2). The doses of 6-MP and oral MTX in Maintenance will be collected to assess the therapy received by patients on each randomized regimen. Exploratory analyses of the TGN and Methyl MP levels will be conducted to study the possible interaction between 6-MP and MTX dosing in Maintenance, and will be used as additional information to evaluate the treatment regimen with higher intensity MTX dosing.

Additional reporting requirements for patients with DS SR B-ALL and DS B-LLy:

In addition to the routine AE required for all patients on this trial, the following additional AEs are required to be reported for patients with Down syndrome:

1. All Grade 3 and higher infectious toxicities
2. Grade 3-4 febrile neutropenia
3. Immunologic Serum IgG levels at the start of each reporting period and whether intravenous infusion of immunoglobulins (IVIG) was administered during that reporting period.

IgG levels and whether IVIG was administered will be collected in order to assess the effectiveness of the supportive care changes implemented on this study. These data will be used to evaluate whether DS patients on this study who suffer severe or fatal infectious complications were hypogammaglobulinemic at the time, and whether they received IVIG replacement. These patients, as well as patients that experience toxic events, will be very few and, hence, these data will be evaluated individually and summarized descriptively.

10.4 Gender and Minority Accrual Estimates

Based on the distribution of patients enrolled on COG AALL0331, the gender and minority distribution of the AALL0932 study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	793	891	1,684
Not Hispanic or Latino	3,481	4,318	7,799
Ethnic Category: Total of all subjects	4,274	5,209	9,483*
Racial Category			
American Indian or Alaskan Native	20	40	60
Asian	131	198	329
Black or African American	220	283	503
Native Hawaiian or other Pacific Islander	19	12	31
White	3,884	4,676	8,560
Racial Category: Total of all subjects	4,274	5,209	9,483*

* These totals must agree.

11.0 EVALUATION CRITERIA

11.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the CTCAE version 4.0 of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the NCI website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Additionally, toxicities are to be reported on the appropriate case report forms.

11.2 Response Criteria for Patients with Leukemia (B-ALL)

See Section 3.3

11.3 Response Criteria for Patients with B-LLy[95,96]

11.3.1 Complete Response (CR)

Defined as disappearance of all detectable clinical evidence of disease from all sites. Lymph nodes must have decreased to less or equal 1.5 cm. This will be determined by physical exam and CT.

For patients with a previous positive PET scan, PET scan must be negative.

A post-treatment residual mass of any size is considered a CR as long as it is PET negative. A negative PET is required in patients with post-treatment residual masses to be considered a CR. Patients with post-treatment residual masses must be followed by PET and remain PET negative to be considered CR.

Bone lesions that remain positive by MRI and/or PET will be considered CR if there is resolution of all surrounding soft tissue component by the end of Consolidation. No new lesions.

11.3.2 Partial Response (PR)

At least a 50% decrease in the sum of the product of diameters (SPD) of the lesions of up to six of the largest dominant nodes or nodal masses. Splenic and hepatic nodules must decrease by at least 50% in their SPD. No new lesions.

In patients with a positive PET scan prior to therapy, the post-treatment PET must be positive in at least one previously involved site.

11.3.3 Stable Disease (SD)
Failure to qualify for a PR or PD. No new lesions.

In patients with a positive PET scan prior to therapy, the PET must be positive at prior sites of disease with no new areas of involvement on the posttreatment CT or PET.

11.3.4 Relapsed/Progressive Disease (PD)
Greater than 50% increase in the size of any lesions or appearance of new lesion(s) more than 1.5 cm in any axis.

In patients with a positive PET scan prior to therapy, lesions must be PET positive.

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 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.

12.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- ***the current known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or***
- ***the drug package insert.***

Secondary Malignancy
A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., 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 CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

12.3 **Reporting of Adverse Events for Commercial Agents** - via CTEP-AERS

Expedited AE reporting must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via https://eapps-ctep.nci.nih.gov/ctepaers

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study Committee roster.

- COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

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.

CTEP-AERS 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			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[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 **CTEP-AERS**.

***Note**: Table A –*CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of an Investigational Agent* has been deliberately omitted as it is not relevant to this study in which only commercial agents are used.

As of August 25, 2010 all secondary malignancies should be reported via CTEP-AERS.

12.4 **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 CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and non-hematologic Grade 4 and higher Adverse Events

as well as the following specific toxicities identified by the ALL Toxicity Reporting Task Force to be collected on all future COG ALL trials.

1. CNS hemorrhage requiring medical intervention (Grade 2 or 3)
2. GI bleed requiring operative or interventional radiology intervention (Grade 3)
3. Pancreatitis requiring medical intervention (Grade 2 or 3)
4. Osteonecrosis interfering with function (Grade 2 or 3)
5 Transient ischemic attacks (All grades)
6. Stroke (All grades)
7. Encephalopathy (Grade 3)
8. Neuropathy; motor or sensory, interfering with ADL (Grade 3)
9. Seizure (Grade 2 or 3)
10. Allergic reaction (Grade 3)
11 Ileus (Grade 3)
12. Mucositis/stomatitis; functional (Grade 3)
13. Bilirubin (Grade 3)
14. Thrombosis (Grade 3)

Additional reporting requirements for patients with DS SR B-ALL and DS B-LLy:

1. All Grade 3 - 4 infections
2. Grade 3 - 4 febrile neutropenia*
3. Immunologic Serum IgG levels at the start of each reporting period and whether intravenous infusion of immunoglobulins (IVIG) was administered during that reporting period.

* **Note**: for EACH infection and febrile neutropenia event reported, the CTCAE event "neutrophil count decreased" should also be reported separately using a new AE form, should it occur. "Neutrophil count decreased" can be found under "Investigations". DO NOT report low platelets or any other low hematologic AE for this study.

13.0 RECORDS AND REPORTING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*".

13.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. 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.

14.0 PATHOLOGY GUIDELINES AND SPECIAL STUDIES FOR B-LLy PATIENTS

14.1 Pathology Goals

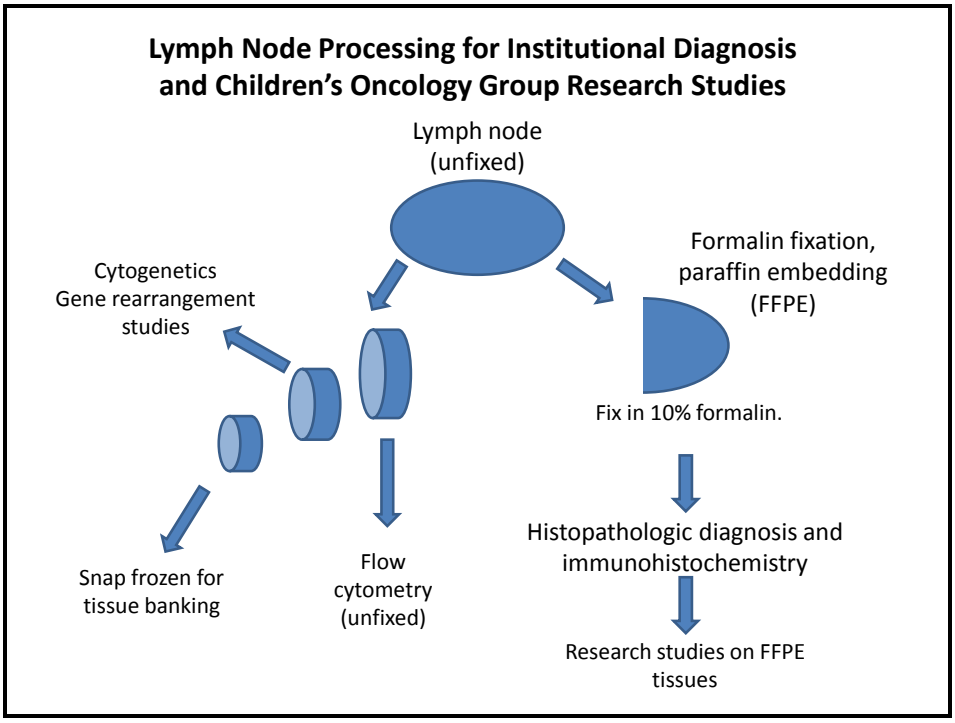
1. Provide quality control by central pathologic review with accurate diagnosis and classification of pediatric non-Hodgkin lymphoma. This is to be based on both morphologic and immunophenotypic criteria. **This study is limited to B-cell lymphoblastic lymphoma**. Patients with T-lineage lymphoblastic lymphoma are not eligible for this study.
2. Employ the 2008 World Health Organization (WHO) Lymphoma Classification[97] to facilitate concordance in diagnosis.
3. Correlate morphologic, immunophenotypic and cytogenetic data for the lymphomas included in this treatment protocol.

14.2 Requirements for Handling Tissue or Cytology Specimens at Primary Institutions

14.2.1 Tissue Specimens

Tissue should preferentially, whenever possible, be obtained fresh and delivered immediately to the Pathology Laboratory for optimal handling and distribution (fixation, snap freezing, cytogenetics, etc.). Refer to diagram entitled "Lymph Node Processing For Institutional Diagnosis And Research Studies In Children's Oncology Group" (Figure 14.1). Submit representative tissue sections for fixation including at least 1 block with 10% buffered formalin.

Figure 14.1



14.2.2 Cytology Specimens

Cytology or body fluid specimens (i.e. pleural fluid) should be delivered promptly to the pathology laboratory, and handled per primary institutional procedures. Sufficient material should be utilized for morphologic evaluation by cytocentrifuge preparations stained with a Romanowsky stain (i.e. Giemsa or Wright's stains). Provided enough specimen is available, at least 1 cell block should be prepared with specification of the fixative utilized (formalin preferred) and the time in fixative.

14.3 Immunophenotyping Recommendations for Primary Institutions

For eligibility in this study, the methodology and criteria for immunophenotypic analysis defined by the submitting institution will be accepted. Recognized methods include: flow cytometry, paraffin section immunohistochemistry, and cytocentrifuge (cytospin) immunocytochemistry. For eligibility in this study, a panel of antibodies should be employed for immunophenotypic evaluation. This can be done on fresh tissue by flow cytometry, on paraffin embedded tissue by immunohistochemistry, and on body fluid/cytology specimens by flow cytometry or cytocentrifuge (cytospin) immunocytochemistry. The panel of antibodies is listed as follows:

T-Cell: CD3.

B-Cell: CD19, CD20, CD22, CD79a, PAX5, Kappa, Lambda.
Myeloid: CD13, CD15, CD33.
Other: CD10, CD34, CD45, TdT.

For cases in which no paraffin embedded tissue has been prepared, and only stained cytospin slides remain available, these cases will be acceptable for protocol submission and pathology review when adequate immunophenotypic data is available from the primary institution. This situation may occur with cases evaluated by cytospin immunocytochemistry or flow cytometry immunophenotyping. If specimen is limited preventing a complete immunophenotypic evaluation, a recommended minimum panel of antibodies should include: CD3, CD19, CD20, Ig kappa, Ig lambda, and TdT. If specimen is limited to paraffin embedded tissue only, a preferred panel of antibodies should include at least: CD3, CD79a, and TdT, and either CD19 or PAX5 as an additional B-cell marker. The method of TdT evaluation should be specified (i.e. flow cytometry or immunohistochemistry). If immunophenotyping studies are not available locally, the case may be sent as a consultation case for evaluation including immunophenotyping studies to Dr. Sherrie Perkins (see address in Section 14.5.6).

14.4 Pathology Staging Criteria

Cerebrospinal Fluid: Leukocyte count greater than or equal to 5/µL, with presence of blasts. TdT evaluation is strongly recommended.
Bone Marrow: The presence of greater than 5% and less than 25% blasts in a bone marrow aspirate, or focal infiltration in a bone marrow biopsy, represents involvement of the marrow by lymphoblastic lymphoma.

14.5 Retrospective Central Pathology Review

14.5.1 Required Materials

Materials to be submitted for retrospective pathology review to the COG Biopathology Center include the following:

1) Initial diagnostic material prior to therapy.
2) Specimens demonstrating relapse of lymphoma at any time.
3) Specimens from residual masses demonstrating residual lymphoma or complete response to therapy.
4) A copy of all final pathology reports (see details in Section 14.5.1.4).
5) Pathology Data Collection Form (Institutional Pathology Form).
6) Transmittal Form.

Please label all materials with the patient's COG patient identification number and the institutional pathology number and block number found on the corresponding pathology report. The materials to be submitted are described below and listed in Table 14-1.

14.5.1.1 Paraffin Blocks

If possible, it is preferred that paraffin blocks be submitted to the COG Biopathology Center. For surgical biopsy specimens, this should include a paraffin block of tissue prepared in 10% Buffered Formalin (as described in Section 14.2.1). For cytology specimens, a paraffin block may be available as a cell block preparation (see Section 14.2.2). If paraffin blocks cannot be submitted, then submit twenty (20) unstained sections (4 microns thick) of unbaked slides air-dried at room temperature from one representative block and two (2) H&E stained slides from each block. These sections should be place on sialinized slides (i.e. Fisher Superfrost Plus).

14.5.1.2 Cytology Slides

When paraffin blocks have not been prepared, a cytologic preparation of one stained, air-dried cytospin slide (i.e. Romanowsky stain such as Giemsa or Wright's stain) and 10 unstained slides should be submitted.

14.5.1.3 Biopsies of Residual Masses
For these biopsy specimens, send a recut slide (hematoxylin and eosin stain) from all of the paraffin blocks for review. The corresponding pathology report should accompany the slides for review.

14.5.1.4 Pathology Reports
A copy of all pathology reports on each case should be submitted. This should include:
1. Final reports of diagnostic biopsy and bone marrow specimens (even if negative)
2. All immunophenotyping reports of diagnostic biopsy and bone marrow specimens (if available); also include copies of flow cytometry histograms (if available)
3. Results of any genotypic studies (i.e. gene rearrangement studies)
4. Results of any cytogenetic (karyotypic) analysis

14.5.1.5 Pathology Data Collection Forms/COG Pathology Center
A separate pathology data collection form (Institutional Pathology Form) should be completed and submitted along with the above materials. Also, indicate the primary institution pathology diagnosis utilizing the 2008 WHO Lymphoma Classification[97] on the data collection form.

14.5.2 Transmittal Form
A specimen transmittal form must be submitted along with the pathology review materials.

14.5.3 Biopathology Center Address
All material submitted for retrospective central pathology review should be sent via regular mail or using your institutional courier account to:

COG Biopathology Center
Nationwide Children‘s Hospital
700 Children's Drive, WA 1340*
Columbus, OH 43205
Phone: (614) 722-2894
Fax: (614) 722-2897

* The room number is required. Packages not listing the room number could be denied and returned to sender.

14.5.4 Paraffin Blocks and Cytologic Slides-Storage/Return
Paraffin blocks and cytologic slides will be retained at the COG Biopathology Center indefinitely, unless the institution requests their return.

14.5.5 Lymphoma Classification
Morphologic evaluation and classification of the study cases will utilize the criteria described in the 2008 WHO Lymphoma Classification.[97] Eligible pediatric lymphomas will be classified as precursor B-cell lymphoblastic lymphoma.

14.5.6 Review Pathologists
For any questions regarding the pathology protocol, please contact:

Sherrie Perkins, MD, PhD
University of Utah and ARUP Laboratories
Department of Hematology
500 Chipeta Way

Salt Lake City, UT 84108
Phone: (801) 581-5854
Fax: (801) 585-3831

TABLE 14-1: MATERIALS TO SEND FOR RETROSPECTIVE CENTRAL PATHOLOGY REVIEW

1. Paraffin Blocks

Send one of the following:

a. Surgical biopsy specimen: One paraffin block (formalin preferred).
b. Cytology cell block: One paraffin block (specify fixative).
c. If blocks cannot be sent, submit twenty unstained and unbaked sections (4 μm) from 1 representative block and 2 (two) H&E stained sections from each block on sialinized slides.

2. Cytology Slides

Send one stained slide (Romanowsky stain) and 10 unstained slides

3. Biopsies of Residual Masses

a. Send a recut slide (hematoxylin and eosin stain) from all of the paraffin blocks from each of these types of biopsy specimens.
b. Send corresponding pathology report.

4. Pathology Reports

Send all of the following:

a. Final reports of diagnostic biopsy and bone marrow specimens (even if negative).
   a. All immunophenotyping reports of diagnostic biopsy, and bone marrow specimens (if available); also include copies of flow cytometry histograms (if available).
c. Results of any genotypic studies (i.e. gene rearrangement studies).
d. Results of any cytogenetic (karyotypic) analysis.

5. Pathology Data Collection Form (Institutional Pathology Form)

6. Transmittal Form

14.6 Optional Minimal Marrow Disease (MMD) Biology Studies

Effective Amendment #5, the Optional Minimal Marrow Disease Biology is closed. Do not collect or submit samples for testing.

14.6.1 Sample Collection.

A single bone marrow specimen will be obtained at diagnosis to assess disease involvement in the bone marrow. This sample will be shipped to the COG ALL Reference Flow Cytometry Lab using the same shipping and handling requirements as B-ALL patients enrolled on this study. Samples are to be shipped to either Dr. Brent Wood at the University of Washington, or Dr. Michael Borowitz at John Hopkins. The Specimen Transmittal Form is to be submitted with each sample submitted to the COG Reference Laboratory. The specimen transmittal form information should always include the name and telephone number of a person designated by the PI to receive calls from the Reference Laboratory directors. The PI's FAX number must also be noted on each sample inclusion form. **Always** include the patient's name, COG number and date of birth on any sample submitted. This is a joint Commission and College of American Pathologists (CAP) requirement. COG ALL Reference Laboratories may be unable to analyze specimens if adequate patient identifiers are not provided. B-LLy samples for the Reference Laboratories are to be

collected in special 15 mL conical tubes (SM) containing EDTA/RPMI as the anticoagulant and media diluent. These tubes will be prepared in the Reference Laboratories and mailed in batches to each participating institution, where they can be stored frozen at -20°C until use. Tubes are stable for 3 months if refrigerated and stable for 1 year if frozen. To request prepared and pre-packaged sample shipping tubes, click on the 'Biopathology Center Application' link on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application. Please select the protocol 'AALL08B1' to order the shipping tubes required for MMD samples. Even though B-LLy patients are not enrolled on 'AALL08B1', the supplies are still ordered through that protocol.

14.6.2 Bone Marrow Collection Procedures for Reference Laboratories for B-LLy.

a. Collect BM into a syringe and transfer the specimen immediately into the 15 mL shipping media conical tube with RPMI/EDTA.
b. Mix well. Up to 5 mL of BM can be placed in one 15 mL tube with RPMI/EDTA. If you don't have shipping media tubes, you can place the BM into large purple EDTA tubes that are commonly available in most hospitals. However, the viability of the cells is greatly enhanced in the shipping media tubes.
c. 5 mL of BM will be sufficient for MMD analysis at diagnosis.

14.6.3 Sample Shipping

B-LLy bone marrow samples for optional MMD studies will be shipped to Michael Borowitz, MD, PhD at the Eastern Flow Cytometry Laboratory or to Brent Wood, MD, PhD at the Western Flow Cytometry Laboratory according to location (see Geographical Sample Distribution map, Section 7.5):

Eastern Flow Cytometry Reference Laboratory
Michael Borowitz, MD, PhD
John Hopkins Medical Institution
Flow Cytometry Lab
Weinberg Building, Room 2300
401 N Broadway
Baltimore, MD 21231-2410
Phone: (410) 614-2968
Fax: (410) 502-1493
Email: mborowit@jhmi.edu

Western Flow Cytometry Reference Laboratory
Brent Wood, MD PhD
SCCA
Hematopathology Laboratory
Room G7-800
825 Eastlake Ave. E.
Seattle, WA 98109-1028
Phone: 206-288-7060
FAX: 206-288-7127
Email: woodbl@u.washington.edu

FOR SAMPLES THAT ARE EXPECTED TO BE DELAYED FOR MORE THAN 48 HOURS - PLACE A COLD PACK (NOT ICE PACK) IN SHIPMENT. ALL TUBES SHOULD BE LABELED WITH AT LEAST THREE PATIENT IDENTIFIERS, INCLUDING THE NAME, DATE OF BIRTH, AND THE COG NUMBER. IN ADDITION, A SPECIMEN TRANSMITTAL FORM AVAILABLE ON THE RDE SHOULD ALWAYS BE SUBMITTED WITH EACH SAMPLE.

Call Reference Laboratory only when shipping a sample to be delivered on Saturday.

Samples for the Flow Cytometry Reference Laboratory should be mailed by FEDERAL EXPRESS PRIORITY (DELIVERY BEFORE 10 AM) using the COG Federal Express account number available at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

14.7 Optional Tissue Banking and Subsequent Biologic Studies

Although the collection of fresh frozen tissue is desirable for tissue banking and potential future studies, the planned biologic studies described below will utilize formalin fixed, paraffin embedded (FFPE) tissues due to the low frequency of receiving frozen tissues in previous trials. Therefore, FFPE specimens will be requested on all cases for the proposed studies, and fresh frozen tissue will be collected for banking when available. Specimens to characterize the biologic nature of the disease will focus on 2 major areas: 1) cytogenetic characterization by FISH and 2) SNP array profiling. Tissue collection is requested prior to treatment initiation and also at the time of relapse. It is anticipated that there will be variability in the type and amount of tissue submitted based upon the accessibility of the tumor tissue and the feasibility of obtaining it (i.e. patients with large masses who are sedation risks and needle core biopsy specimens will be expected to have limited tissue available). Minimum requirements for study entry will include sufficient tissue to confirm the diagnosis. All available biologic specimens will be sent to the COG Biopathology Center, which will serve as the central repository for this component of the study. The study committee will assess the state and quantity of material for subsequent studies with allocation to designated laboratories, placing priority in the studies in the rank order listed below. The collection, processing, shipping and analysis of the tissue have been incorporated into the AALL0932 protocol in order to prevent any modification or amendment of the ALL Classification Study (AALL08B1) or Project:EveryChild (APEC14B1). Specific details of the biologic studies include:

1. *Cytogenetic Analysis*: Limited cytogenetic analysis (via FISH) will be pursued in all specimens with sufficient tissue given the great paucity of data available characterizing the nature of cytogenetic abnormalities in B lymphoblastic lymphoma (B-LLy). Conventional cytogenetic analysis on fresh tissue will not be attempted as prior studies have failed to yield sufficient specimens to warrant a commitment of resources to this endeavor. FISH targeted at genetic lesions known to characterize B-ALL combined with SNP array studies below will allow a more detailed characterization of the genetic abnormalities in B-LLy and comparison to the genetic abnormalities of B-ALL.

2. *SNP Array Profiling*: We have recently piloted the feasibility of high resolution single nucleotide polymorphism (SNP) analysis to characterize gene copy number alterations and allelic imbalance in B-LLys using DNA isolated from FFPE tissues. The ability to use fixed tissue to assess genetic alternations will expand the ability to study genetic alterations in B-LLy, which have been difficult to assess due to the limited tissue typically available for cytogenetic analysis. Based upon the availability of resources, a targeted approach will be expanded to gain more extensive characterization of the incidence of genetic aberrations in B-LLy and their correlation to clinical outcome. This may potentially lead to insight of the important genetic features of high risk disease and possibly reveal potential targets for new therapies.

For cases with a limited amount of tissue available for analysis, the AALL0932 and NHL Biology Committee will prioritize specimens for studies.

14.8 Preparation of Tissue Banking Samples at Time of Diagnosis or Relapse

For every case, even if frozen tissue is obtained, FFPE tissue should be submitted by sending a representative block. If this is not possible, then ten 5 µm unstained slides should be submitted for FISH, and two 50 µm tissue sections (100 microns total) should be cut and submitted in a cryovial similar to how

fixed tissue would be submitted for a PCR-based clonality assay. When fresh tissue is available at diagnosis for banking, at least one square centimeter of snap frozen tumor is requested in addition to the material required for central review (described in Section 14.5). If more than 1 gram is available, cut tissue into 1 gram aliquots. Wrap each aliquot of tissue in a piece of foil and snap freeze in vapor phase liquid nitrogen (do not submerge the tissue in the liquid nitrogen) or on dry ice. Place frozen tissue in zip lock bag. Using a waterproof marker, label the bag with the patient's BPC number, specimen type and date obtained. Store specimens at -70°C or colder until shipped. Include a transmittal form with each shipment of specimens. If tumor tissue is obtained at the time of relapse for clinical purposes, additional material (as described above for diagnosis) is requested for banking and subsequent biologic studies. The Biopathology Center (BPC) will bank the tissue for future distribution and use including the studies listed above.

14.8.1 Specimen Shipping Instructions

Specimen Procurement Kits for shipping frozen tumor tissue to the BPC for AALL0932 are provided upon request. To request a Specimen Procurement Kit,access the BPC Kit Management system: https://ricapps.nationwidechildrens.org/KitManagement/ Specimen procurement kits must be shipped to the BPC, Monday through Thursday for delivery Tuesday through Friday.

1. Before the frozen tissue is placed into the Specimen Procurement Kit, it must first be placed in 3 separate layers of packaging:
   a. Place the tissue in a zip lock bag.
   b. Place the zip lock bag in the plastic watertight biohazard diagnostic envelope and seal the envelope securely.
   c. Place the clear plastic biohazard diagnostic envelope inside the pressure-proof Tyvek diagnostic envelope and seal securely.

2. Place the tissue inside the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full.

3. Place the transmittal form inside the compartment.

4. Place the Styrofoam lid on top to secure specimens during shipment.

5. Close the outer lid of the Specimen Procurement Kit and tape with filament or other durable sealing tape.

6. Access the BPC Kit Management system at:

   https://ricapps.nationwidechildrens.org/KitManagement/

   Print a Federal Express shipping label. A blank adhesive label is provided in the Specimen Procurement Kit to use when printing the shipping label. Attach the shipping label to the top of the kit. Complete the dry ice label (UN 1845). Stick the dry ice and Exempt Human Specimen labels to the side of the kit. Arrange for Federal Express pick-up per your usual institutional procedure or by calling 1(800) 238-5355.

   Ship specimens to:
   COG Biopathology Center
   Nationwide Children's Hospital
   700 Children's Drive, Room WA1340*
   Columbus, OH 43205

Phone: (614) 722-2865

* The room number is required. Packages not listing the room number could be denied and returned to sender.

14.9 Optional Studies of Genomic Variation

14.9.1 Sample Collection

A blood sample at Day 29 is being requested specifically for the purpose of providing constitutional (germline) DNA from each B-LLy patient. Whenever possible, an aliquot of diagnostic BM or PB will also be set aside for extraction of somatic tumor DNA. In some cases, RNA may be used as the starting material.

Peripheral Blood Collection Procedures for Reference Laboratories for B-LLy:

a. For studies of genomic variation, 5 mL of PB on Day 29 should be placed in plastic, purple, EDTA tubes. **DO NOT SHIP SYRINGES**.

Specimen	Study	Laboratory
Peripheral blood 5 mL	Studies of Genomic Variation	Molecular Reference Laboratory

14.9.2 Sample Shipping

B-LLy peripheral blood samples will be shipped to the Molecular reference laboratory.

Molecular Laboratory

Julie Gastier-Foster, PhD
COG ALL Reference Laboratory
Nationwide Children's Hospital
700 Children's Drive, C1961
Columbus, OH 43205
Contact Person: Yvonne Moyer
Phone: (614) 722-2866
Fax: (614) 722-2887
Email: Julie.Gastier-Foster@nationwidechildrens.org

FOR SAMPLES THAT ARE EXPECTED TO BE DELAYED FOR MORE THAN 48 HOURS - PLACE A COLD PACK (NOT ICE PACK) IN SHIPMENT. ALL TUBES SHOULD BE LABELED WITH AT LEAST THREE PATIENT IDENTIFIERS, INCLUDING THE NAME, DATE OF BIRTH, AND THE COG NUMBER. IN ADDITION, A SPECIMEN TRANSMITTAL FORM AVAILABLE ON THE RDE SHOULD ALWAYS BE SUBMITTED WITH EACH SAMPLE.

Call Reference Laboratory only when shipping a sample to be delivered on Saturday.

Samples for the Molecular Reference Laboratory should be mailed by FEDERAL EXPRESS PRIORITY (DELIVERY BEFORE 10 AM) using the COG Federal Express account number available at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

15.0 THE PATIENT LEUKEMIA EXPERIENCE ANCILLARY STUDY:

ASSESSMENT OF BURDEN OF THERAPY FOR CHILDREN WITH AVERAGE RISK ACUTE LYMPHOBLASTIC LEUKEMIA (AR B-ALL) ENROLLED IN COG AALL0932 AS MEASURED BY, PATIENT QUALITY OF LIFE, MISSED SCHOOL/WORK, AND PARENT'S

PERCEPTION OF HEALTH VULNERABILITY, PHYSICAL FUNCTIONING, AND EMOTIONAL DISTRESS

15.1 **Correlative Study Design**:

As of April 19, 2013, the PLES has met accrual goals and is closed to new patient enrollment. However, institutions are required to continue data collection at remaining evaluation time points, for patients already enrolled on this study.

15.1.1 Eligibility Criteria:

1. Enrolled on AR B-ALL post-Induction arm of AALL0932.
2. At least one parent must have speaking and writing knowledge of English (because of instrument availability).
3. Age ≥ 4 years at time of study consent (validated age ranges of instruments).
4. No history of pre-leukemia diagnosis of neurodevelopmental disorder (i.e. Down syndrome, autism, seizure disorder).

15.1.2 Consent

This Patient Leukemia Experience (PLE) ancillary study is embedded in the AR arm of AALL0932. Consent for this study is incorporated into the consent for the AR arm, which occurs at the conclusion of Induction therapy. Patients who enroll on the AR arm of AALL0932 can elect to enroll on this ancillary study as an option, not a requirement.

15.1.3 Data Collection

The required observations for enrollees on the Patient Leukemia Experience ancillary study are included on AALL0932 roadmaps. At the scheduled time points (described below), the study surveys are completed by parents. The surveys are administered at the time of the clinic visit in hard copy and completed by the end of the clinic visit. Institutions receive these survey tools by email upon enrollment to this correlative study. In addition, the gender-specific survey instruments are located in the Data Collection/Specimens section of the AALL0932 protocol webpage. To insure data fidelity, except for the BASC-2 PRS, data will be entered systematically by the clinical research associates (CRAs) via the RDE system. The BASC-2 PRS data forms will be sent to COG via DocuSam by the CRA's at which time the researchers at the Yale site will enter the data. For any issues related to the ancillary study, contact may be made to Moira Whitley (moira.whitley@yale.edu) or the Patient Leukemia Ancillary Study Chair, Dr. Kadan-Lottick (nina.kadan-lottick@yale.edu)

The total time needed to complete the assessments will be about 25 - 35 minutes for each of the first four time points and about 60 minutes for the last time point, which is a similar length of time in the currently successful AALL0331 ancillary study. The instruments were selected based on extensive validation in children with cancer and/or life-threatening illness, sensitivity to treatment related burdens relevant to the proposed therapies, ease of administration by ancillary staff and brevity:

1) Baseline Demographic/Family Survey (~10 minutes) (PLE Demographics Questionnaire): Questions related to education, family income, and family structure; are completed by parent.

2) Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL 4.0) (< 4 minutes): (PLE Form A) 23 items with responses on 5 point Likert scale. This instrument measures the child's quality of life, yielding separate scales for physical, emotional, social, and school functioning. The Parent Version (validated for ages ≥ 2 years) is administered for all participants.[98]

3) Family life with Leukemia Survey (10 minutes): (PLE Form B) Asks the parents questions regarding the family's school and work status.

4) The Family Assessment Device (FAD) - General Functioning Subscale (~5 minutes): (PLE Form C) This is an extensively used questionnaire to assess family functioning, including that of hospitalized children experiencing chronic illness.[99] Parents rate the extent to which each statement describes their family on a 4 point scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*). Cutoff points for unhealthy family functioning[100,101] and reliability has been established.[102] The General Functioning Subscale relies on 12 questions.

5) Child Vulnerability Scale (~ 5 minutes): (PLE Form D) The parent completes the Child Vulnerability Scale[103], which assesses parent's perceptions of children's general vulnerability to health problems. This 8 item scale uses a 4 point Likert scale ranging from 0 (*Definitely False)* to 3 (*Definitely True)*. A sample item includes "I often think about *calling the doctor about my child."* The scale is scored by summing responses and higher scores reflect greater perceived vulnerability. The Child Vulnerability Scale has an internal consistency alpha of 0.74[103] and a test-retest reliability coefficient of 0.84.[104]

6 Behavior Assessment Scales of Children – Second Edition, Parent Rating Scale (BASC-2 PRS) (~10-20 minutes): (PLE Form E) The parent completes the BASC-2 PRS[29], a questionnaire that assesses the emotional (e.g. anxiety, depression, somatization), behavioral (e.g. hyperactivity, aggression, withdrawal), and adaptive functioning (e.g. social skills, functional communication, adaptability) of children and adolescents. The BASC-2 PRS contains 134 - 160 items and uses a 4 choice response format. Scores are scaled so that a T-score greater than or equal to 70 is clinically significant and a T-score between 60 and 69 falls within the at risk range. For the Adaptive Scale a T-score under 30 is clinically significant. Assessment with this tool will be performed only at the last data collection point – i) Eighteen months after the beginning of Maintenance (off therapy time point for girls, ii) Thirty months after the beginning of Maintenance (off therapy time point for boys; girls will not be evaluated at this time point).

15.1.4 Evaluation Schedule

There will be 5 time points for collection of data (4 for girls; 5 for boys):

1. End of Consolidation (~ 2 months after diagnosis): sometime between Day 15 of Consolidation and prior to Day 1 of Interim Maintenance I
2. End of first month of Maintenance (~ 8 months after diagnosis - Day 29 of Maintenance Cycle #1)
3. Ten months after beginning of Maintenance (Day 29 of Maintenance Cycle #4)
4. Eighteen months after beginning of Maintenance (off-therapy time point for girls; Day 29 of Maintenance Cycle #7 for boys)
5. Thirty months after beginning of Maintenance (off-therapy time point for boys; girls will not be evaluated at this time point)

The end-Consolidation is the first feasible time point to get a baseline evaluation because average risk status will not be determined until the end of Induction. The first time point may be completed as early as Day 15 of Consolidation to as late as Day 29 of Consolidation/Day 1 of Interim Maintenance I so all patients are at least 2 weeks after the previous dose of vincristine and at least 3 weeks after completion of the dexamethasone pulse. For the other time points, there will be a 1 month grace period to collect the data, i.e. data must be collected at the designated time point or within 1 month *after* that time point. If the evaluation day also includes intrathecal chemotherapy, the evaluation will be done prior to the procedure.

Table 15.1.4.1

	Demographic Questionnaire (PLE Demographics questionnaire)	PedsQL (PLE Form A)	Family Life with Leukemia (PLE Form B)	Family Assessment Device (PLE Form C)	Child Vulnerability Scale (PLE Form D)	BASC- 2 PRS (PLE Form E)
End of Consolidation (After Day 15, but before start of IM#I)	X	X	X	X	X	
End of first month of Maintenance (Day 29 of Maintenance Cycle #1).		X	X	X	X	
Day 29 of Maintenance Cycle #4		X	X	X	X	
Day 29 of Maintenance Cycle #7 (boys)/End of therapy (girls)		X	X	X	X	X (girls only)
End of therapy (boys)		X	X	X	X	X

15.2 **Specific Hypotheses**

The treatment of pediatric cancer poses a significant burden to the child and their family. We propose to assess this burden by quantifying the following elements related to care: 1) patient quality of life, including emotional distress and physical functioning, 2) missed days of school/daycare by patients and work by parents, and 3) parent perception of the child's health vulnerability.

A child's physical, emotional, school, and peer functioning can all be disrupted by the acute toxicities of specific therapeutic agents as well as the need to miss school and interaction with peers which treatment demands. Certain chemotherapy agents have been shown to adversely affect emotional and physical functioning, aspects of the child's quality of life. Specifically, dexamethasone and vincristine are associated with pain from myopathy[19] and peripheral neuropathy, respectively.[20] Further, dexamethasone is also associated with emotional liability, aggressive behaviors, and depression.[105] Dexamethasone therapy has been associated with depression and anxiety in the clinically distressing range during therapy in about 30% - 45% of ALL patients.[26,105] About 45% of children enrolled on the HRQOL component of AALL0331 have depression symptoms in the at-risk/clinical range at the beginning of Maintenance, several weeks after the last dexamethasone pulse (Kadan-Lottick, 2009, unpublished data).

Rates of absenteeism are 4 times higher for children with cancer as compared to the general school-age population, missing 21 to 45 days of school per year.[106-108] Intermittent and prolonged absences from school are disruptive to the child's academic progress and social relationships, particularly for those children who had learning or social vulnerabilities prior to the cancer diagnosis.[109-111] While some medical professionals may urge parents to maintain normalcy by keeping their child in school and participating in social activities, parents have expressed the considerable difficulty in doing so given hospital visits, changes in mobility and the need to manage symptoms and painful procedures.[112]

Children with serious illnesses such as leukemia are at increased risk of being viewed as abnormally susceptible to illness or death, even after they are fully recovered.[103,104] The term *vulnerable child* describes a child who is perceived in this way by his/her parents. Continued parental fears can result in abnormal interactions between the parents and their child that in turn adversely affect normal child development.[27] For example, children who are perceived as vulnerable have been shown to avoid school and have more

internalizing problems, including separation and social anxiety.[110,111,113,114] Studies in premature infants, children hospitalized for infectious illnesses, and infants with congenital abnormalities suggest that it is the parents' understanding and beliefs about the problems that determines perceptions of vulnerability, not what is understood by the physician. Parents whose children are randomized to less intensive therapy during Maintenance may be more reassured that their child is on a positive trajectory to recovery.

The nonmedical burden of illness to families of children with cancer can be substantial.[31,115,116] Many families experience lost income or productivity associated with providing care to the child.[31] In one United States study of 70 families of children with cancer, over half of the families experienced financial hardship amounting to more than 20% of the weekly family income.[117] Many parents, mainly mothers, will resign or reduce outside employment in order to care for their child.[30,116]

In assessing average risk patients, overall, we will generate needed data that will inform future intervention studies to provide supportive care in the domains most affected for patients and their family. Specifically, we will learn the optimal timing of interventions for the non-survival outcomes that are most impacted.

15.3 **Specific Aims**

Specific Aim 1: To assess prospectively the burden of AR B-ALL therapy in children enrolled in COG AALL0932 compared to published normative data, with respect to the following:

1. Child's quality of life as reported by parent
2. Missed days of school/daycare/work by patients and their parents
3. Parental perception of the child's health vulnerability
4. Physical functioning in daily age-appropriate activities
5. Emotional functioning

Specific Aim 2: To compare the relative burden of AR B-ALL therapy in children randomized to every 4 week (Arm A and B) vs. every 12 week (Arm C and D) dexamethasone/vincristine pulses during Maintenance on COG AALL0932 as measured by the child's quality of life, missed days of school/daycare/work by patients and their parents, parental perception of the child's health vulnerability, physical functioning, and emotional functioning, standardized to published normative data on validated instruments.

15.4 Statistical Design

Specific Aim 1

The first specific aim is to evaluate whether or not children treated for Average Risk B-ALL have clinically significant impairment in the child's quality of life (measured by PedsQL), missed days of school/daycare/work by patients and their parents, parental perception of the child's health vulnerability (assessed by Child Vulnerability Scale), and emotional functioning (measured by the BASC-2 PRS). The primary data analysis will be of PedsQL scores. Standardized scores for the sub-scales of the PedsQL 4.0 will be calculated using age and gender specific normative data. Values will be age and, where appropriate, gender standardized, and compared between the children with ALL and the population normative values with a one-sample t-test.[118] If the data are not normally distributed, a non-parametric equivalent will be used.[119] To achieve over 90% power with a two sided alpha level of 0.001 (adjusted for multiple comparisons); we require a sample size of 169 children to detect a 0.3 standard deviation difference between the children with ALL and the published normative values on each of the sub-scales at each of the time points.

Specific Aim 2

The second specific aim seeks to determine how child quality of life measures in children with Average Risk B-ALL vary as a function of randomization to every 12 weeks or every 4 weeks DEX/VCR pulses during Maintenance. The overall objective is to identify (1) if every 12 weeks DEX/VCR pulses results in enhanced quality of life compared to every 4 weeks DEX/VCR pulses at 2 (girls) or 3 (boys) time points during Maintenance and at the end of therapy. Assessments of the child will be completed beginning with a baseline prior to the start of Maintenance therapy at the end of the Interim Maintenance II phase of therapy. The first time point will be used as a baseline to confirm that functioning in the 2 therapy groups is similar prior to the start of Maintenance therapy; data from the subsequent 3 time points will be the outcomes of interest. We will compare differences in means (of the continuous measures) between the 2 randomization groups with 2 sample t-tests. Values will be normalized for age and gender prior to comparison. If the continuous data are not normally distributed, a non-parametric statistical measure will be used.

The primary data analysis will be of Pediatric Quality of Life Instrument scores. Standardized scores for the sub-scales of the Pediatric Quality of Life Instrument will be calculated using age and gender specific normative data. The primary analysis will consist of comparing scaled outcomes in the 4 separate domains of emotional, physical, school, and social functioning at the 3 repeated measures, adjusted for age, gender, and family income. Sample size calculations based on a 2-sided alpha level of 0.01 (to adjust for the multiple comparisons of 4 sub-scales of quality of life) to achieve 90% power. A minimum sample of 240 patients in each of the post-Induction groups is needed in a design with 3 repeated measurements having a Compound Symmetry covariance structure when the standard deviation is 1, the correlation between observations on the same subject is 0.5, and the alpha level is 0.01, to detect group differences of 0.3 standard deviations. This difference is validated as being in the small to moderate effect size range.[98]

Data analysis will also be done to compare missed days of school/daycare by patients and work by parent, family functioning, measured by the FAD, parent perception of child vulnerability (measured by the Child Vulnerability Scale), and emotional symptoms (measured by the BASC-2 PRS), adjusting for age, gender, and family income.

It is not a specific aim to examine quality of life outcomes in patients randomized to the different methotrexate doses. Methotrexate was not associated with physical or emotional impairment at the higher 40 mg/m^2/week oral dose during continuation therapy in a study of 243 children with ALL enrolled in the Dallas-Fort worth protocol, except for largely self-limited sub-clinical transaminitis[11] Oral methotrexate has been associated with subtle changes in the attentional and executive functioning domains of neurocognitive functioning, but typically these changes develop years after diagnosis and require

standardized performance-based neuropsychological instruments for detection.[71,120] We would not expect any detectable differences during therapy and with a self-reported instrument. To verify that oral methotrexate is not associated with the measured quality of life outcomes, we will perform post-hoc analyses comparing the 20 mg/m^2 (groups A and C) and 40 mg/m^2 (groups B and D) oral methotrexate groups.

Patient Accrual:
Based on recently observed attrition rates of about 25% on the HRQOL component of COG AALL0331 due to relapse, death, and study withdrawal, 276 patients in each of the two randomization groups (600 overall) will be required to adequately assess Specific Aim 2 and is more than adequate for Specific Aim 1. As stated above in the description of the therapeutic study, a total of 2996 AR patients will be accrued over 4.9 years. Based on past studies, we estimate that 90% are English speaking and 90% are at least 4 years of age, yielding 1,747 potentially eligible participants (364 per year) for the AR B-ALL ancillary study. Assuming 75% participation on this ancillary study, the needed 600 patients will be enrolled in approximately 20 months corresponding to a 30 patient/month enrollment rate.

15.5 **Significance**

Cancer treatment is a burden to children and their families in terms of the parents' perception of their child's vulnerability, the child's general quality of life including emotional distress and physical functioning, and the disruption to the child and family. This includes school and work absenteeism, which has implications for academic progress and adequate socialization for the child, as well as economic loss for the parent and family. These concepts have been understudied among those children undergoing average risk treatment for ALL. Quantifying the extent to which these areas are affected in children and their families will directly inform the development of interventions designed to ameliorate their impact, including their timing and focus.

In addition, we will have the data to compare severity of these issues between patients on a dexamethasone/vincristine pulse schedule of every 4 weeks versus every 12 weeks. This comparison will be especially useful to inform future clinical trials if event free survival does not differ significantly between the two arms, but the burden of therapy is worse in one or the other arm. Because we will have standardized, informative data regarding the burden of therapy, we will have sufficient data to plan future intervention studies to ameliorate functional outcomes regardless of which regimen moves forward in subsequent therapeutic studies.

16.0 THE LEUKEMIA PHYSICAL FUNCTIONING STUDY: LONGITUDINAL ASSESSMENT OF PERIPHERAL NEUROPATHY AND MOTOR FUNCTION IN CHILDREN TREATED FOR AVERAGE RISK ACUTE LYMPHOBLASTIC LEUKEMIA (AR B-ALL)

16.1 Correlative Study Design:

As of March 15, 2013, the LPFS has met accrual goals and is closed to new patient enrollment. However, institutions are required to continue data collection at remaining evaluation time points, for patients already enrolled on this study.

16.1.1 Eligibility Criteria:

1. Enrolled on the Average Risk arm of AALL0932 at one of the limited participating sites (available on the AALL0932 protocol webpage) within the Children's Oncology Group
2. At least 1 parent must have speaking and writing knowledge of English or Spanish
3. Age ≥ 3 years at time of study consent (age ranges of instruments used in validation or other studies)
4. No history of neurodevelopmental disorder prior to leukemia diagnosis (i.e. Down syndrome, autism, seizure disorder)

16.1.2 Consent

This Leukemia Physical Functioning ancillary study is embedded in the AR arm of the AALL0932 therapeutic study. Consent for this study is attached in an amendment into the consent for enrollment on the AR Arm, which occurs at the conclusion of Induction therapy. Patients who enroll on the average risk arm of AALL0932 can elect to enroll on this ancillary study as an option, not a requirement.

16.1.3 Data Collection

The required observations for enrollees on the neuropathy ancillary study are included on AALL0932 roadmaps. At the scheduled time points (described below in 16.1.4), which coincide with regularly scheduled clinic visits, participants will undergo an approximately 45 minute functional and parent-report evaluation by a pediatric physical therapist or occupational therapist. All measures are widely-used, non-invasive assessments that would be within the scope of practice of any licensed physical therapist or occupational therapist that assesses children in the clinical setting. The assessments were chosen to measure all of the key elements of chemotherapy associated neuropathy in a valid fashion, but without redundancy. We included complementary assessments of actual day to day functioning by performance tests and parent report. Institutions receive the data tools by email upon enrollment to this correlative study. In addition, the gender specific survey instruments are located on the Data Collection/Specimens section of the AALL0932 protocol webpage. Data entry occurs via eRDES. For issues related to the ancillary study, contact may be made to Moira Whitley (moira.whitley@yale.edu) or the Leukemia Physical Functioning Study Chair, Dr. Nina Kadan-Lottick (nina.kadan-lottick@yale.edu).

The following table displays the evaluation of standardized measures that will be completed at each of the 4 time points:

Table 16.1.3.1. Assessment of Peripheral Neuropathy and Motor Function

Parameter Assessed	Test/method	Time to Complete (minutes)
Peripheral Sensation in the upper and lower extremities	Peripheral assessment using the Semmes Weinstein monofilaments (SWM)	5
Peripheral vibratory perception in the upper and lower extremities	Vibration using a 128 Hz Rydel-Seiffer tuning fork	3-5
Peripheral motor functioning in the upper extremities	Handgrip strength assessed by a dynamometer (exclude if < 4 years at evaluation time point)	2
Peripheral motor functioning in the lower extremities	Isometric ankle dorsiflexion strength assessed by a myometer	10
Flexibility in the lower extremities	Active and passive ankle range of motion assessed by a goniometer	5
Proximal motor functioning	Sit-ups and push-ups (if ≥ 4 years at evaluation time point) Manual assessment of proximal muscle strength (if 3 - 3.9 years at evaluation time point)	3 - 5
Fine motor dexterity in the upper extremities	Purdue Pegboard	5
Lower extremity daily function	6 Minute Walk with timer.	10
Child report of child's pain and other sensory symptoms	Sensory Symptoms question from the Pediatric-Modified Total Neuropathy Scale	3
Parent report of child daily physical functioning	Pediatric Outcome Data Collection (PODCI) Instrument	15 (completed by parent)
Parent report of child's quality of life	Pediatric Quality of Life Inventory (PedsQL) instrument	5 (completed by parent)
Total duration: ~ 45 minute functional evaluation (with 25 minute concurrent parent surveys)		

The approximately 45 minute evaluation will be done in the order described in the table above to ensure reliability across examiners, patients, and time points. For Spanish speaking patients, the hands-on evaluation will be done with translation by an interpreter. The 2 parent report instruments are validated in Spanish, as well as English. The parent report instruments will not extend the time of the evaluation because they will be completed by the parent concurrently while the child is undergoing the functional evaluation.

The physical therapists will complete a brief clinical research form at the time of each evaluation recording the history of physical therapy and occupational therapy since the last evaluation (or since diagnosis at the first time point) including the indications, frequency, and duration.

Different aspects of actual day to day functioning are assessed with a combination of performance-based and parent report measures: the Purdue Pegboard, the 6 Minute Walk, the PODCI parent-report instrument, and the PedsQL parent-report instrument. The Purdue Pegboard is a measure of fine motor dexterity which is needed in many activities of daily functioning such as buttoning, dressing, and playing with small objects.[121] Walking is an essential lower extremity motor activity of individuals of all ages > 2 years. Parent report of specific age-appropriate activities and quality of life provide insights that may not be elicited during the physical therapy evaluation, but which reflect meaningful impairment.

To help distinguish between corticosteroid-associated myopathy and vincristine-associated neuropathy, we will assess the patient's ability to do sit-ups and push-ups for patients ≥ 4 years, for which there are normative data. These tasks rely almost entirely on *proximal* strength functioning and are impaired in steroid-associated myopathy. For patients 3.0 - 3.9 years of age, proximal strength in the upper and lower extremities will be assessed manually and rated from zero (no movement) to five (normal power). Myopathy is characteristically symmetric proximal weakness that may or may not be associated with

muscle pain and cramps.[122] In contrast, vincristine associated neuropathy is usually peripheral in distribution and would more likely affect fine motor functioning, handgrip strength, ankle strength, and ankle range of motion. In terms of discomfort, vincristine associated neuropathy typically presents as paresthesias in the distal extremities, and rarely pain.[123] We will ask the children to report on their sensory symptoms with a short question from the Pediatric-Modified Total Neuropathy Scale that asks if "any parts of your body are tingly, numb (can hardly feel), or hurt" and the location of symptoms reported.[124] Because the definitive tests of nerve and muscle biopsy would be too invasive,[122] we will rely on the pattern of deficits to help distinguish neuropathy from myopathy. Impairment in proximal strength without peripheral involvement will be categorized as myopathy. Impairment in peripheral strength without proximal involvement will be categorized as neuropathy. Concomitant proximal and peripheral impairment will be categorized as indeterminate with likely contributions by both myopathy and neuropathy.

The sit-ups/push-ups and handgrip measures only have normative data for children ≥ 4 years (see further details about each measure below). These 2 measures will be excluded for patients who are not yet 4 years at the evaluation time point. As discussed above, for patients 3.0 to 3.9 years of age, proximal strength in the upper and lower extremities will be assesses manually and rated from zero (no movement) to five (normal power). This will only affect children enrolled at the age of 3.0 to 3.9 years for the first, and possibly the second, time point(s).

Measures included in the focused evaluation have established validity in young children with peripheral neuropathy, availability of standardized normative data, a history of successful administration in both the research and clinical settings, and, when available, past studies in children with cancer and/or life-threatening illness.

16.1.4 Evaluation Schedule

There will be 4 time points for collection of data

1) Between Day 15 of Consolidation Phase and prior to Day 1 of Interim Maintenance I
2) End of first month of Maintenance Phase (Day 29 of Maintenance Cycle #1)
3) 18 months after starting the Maintenance Phase (Day 29 of Maintenance Cycle #7 for boys and end of therapy for girls)
4) 12 months after end of therapy (both boys and girls)

The beginning of Consolidation is the first feasible time point to get an evaluation because average risk status will not be determined until the end of Induction. The first time point will measure the effects of the first 5 almost weekly vincristine doses. Time point 2 will assess the effect of 14 doses of vincristine during the 24 weeks of Interim Maintenance I, Delayed Intensification I, and Interim Maintenance II, and the first 4 weeks of Maintenance. By specifying Day 29 of Cycle #1 of Maintenance (i.e. time point 2), all patients will be approximately 4 weeks after the last dose of vincristine and will not be scheduled for a procedure that day. Time points 3 will indicate how functioning varies during monthly vs. every 3 month vincristine therapy. Time point 4 will represent the 12 month off-therapy evaluation for girls and boys to measure whether any impairment is persistent in the immediate off-therapy period.

The first time point may be completed as early as Day 15 of Consolidation but prior to Day 1 of Interim Maintenance so all patients are at least 2 weeks after the previous dose of vincristine and at least 3 weeks after completion of the dexamethasone pulse. In extraordinary circumstances, a one week grace period can be allowed for the collection of first time point data after obtaining LPFS Study Chair approval (nina.kadan-lottick@yale.edu). For the other time points, there will be a 1 month grace period to collect the data, i.e. data must be collected at the designated time point or within 1 month *after* that time point. If the evaluation day also includes intrathecal chemotherapy, the evaluation will be done prior to the procedure.

16.1.4.1 Table of measures administered at specific time points:

	Physical Therapist/Occupational Therapist Intake Form	Sensory and Motor Symptoms Assessment (LPFS Form A)	Physical Functioning Therapy Assessments (LPFS Form B)	(PODCI) (LPFS Form C)	PedsQL (LPFS Form D)
End of Consolidation (After Day 15 but before start of IM#I)	X	X	X	X	X
End of first month of Maintenance (Day 29 of Maintenance Cycle #1).	X	X	X	X	X
~18 months after starting Maintenance (Day 29 of Maintenance Cycle #7 for boys) End of therapy for girls	X	X	X	X	X
12 months after end of therapy for both boys and girls	X	X	X	X	X

16.1.5 Strategies to Enhance Feasibility and Data Fidelity

Limited institutions within the COG were chosen to participate in this study primarily based on the availability of physical therapists who are expert in assessing chemotherapy-associated peripheral neuropathy and success with previous ancillary studies of non-survival outcomes.

We conservatively estimate that 75% of patients who enroll on the average risk component of the therapeutic study at centers participating in this HRQOL study will also consent to the neuropathy ancillary study. An ongoing, multi-site interventional study of neuropathy in children undergoing therapy for acute lymphoblastic leukemia has enrolled 27 of the 28 eligible patients to date (RO1CA129384 [Ness-Co-Investigator], Dr. Kirsten Ness, personal communication, May 10, 2010). Also, for the current standard risk ALL therapeutic study in COG, AALL0331, almost 90% of eligible patients have enrolled on the embedded health related quality of life ancillary study (Buchanan et al., Abstract presented at American Society of Clinical Oncology in Chicago, IL, 2008). Therefore, we believe that our projections are reasonable and our study is feasible.

Site principal investigators at the selected institutions are oncology or nursing investigators known to be committed to enrolling patients on studies of physical functioning outcomes in cancer patients. Sites were not considered if they had competing research protocols that would potentially influence the development of peripheral neuropathy in ALL patients (e.g. neuropathy intervention studies), or if they did not have adequate clinic time and/or space to do the required study observations.

At the beginning of the study, the responsible physical therapist or occupational therapist from each participating site will review a DVD explaining study procedures that will be prepared by Dr. Ness. In this DVD, Dr. Ness will demonstrate all the study assessments on a model patient and explain how to handle frequently handled challenges. In the DVD, overall education regarding study procedures and quality control of data will be described. The physical therapist (or occupational therapist) at each site will be required to achieve 90% proficiency on a written test of study procedures after reviewing the DVD. Dr.

Ness will communicate individually with therapists who require additional assistance to achieve the target proficiency goal.

A comprehensive manual describing the step-by-step procedures used to collect, record, store, transmit and manage data will be provided for each site. The physical therapists will also undergo yearly performance reviews on their proficiency with the study procedures. As stated above, all measures are routinely used assessments that would be within the scope of practice of any licensed physical therapist or occupational therapist who evaluates children for movement disorders in the clinical setting. To maintain data fidelity, therapists will participate in quarterly conference calls to discuss study progress and challenges.

16.2 Background and Specific Hypotheses

16.2.1 Background

Recent COG trials data project that children with Average Risk Acute Lymphoblastic Leukemia (ALL) will have 5 year event free survival rates of 90% - 95%. Because most patients are anticipated to be long-term survivors, optimal care includes the identification and clinical management of the toxic effects of chemotherapy severe enough to negatively quality of life. A 2009 review of 28 studies evaluating physical activity and exercise during childhood cancer treatment found considerably reduced physical activity during and after treatment.[125] This review emphasized the need for exploration into the pathology underlying these deficits.

Vincristine is an established and integral component of therapy for childhood ALL. Unfortunately, vincristine is also associated with acute and long term peripheral neuropathy that can adversely affect the fine motor skills needed in learning[18] and gross motor abilities important to mobility.[32,126] Although peripheral neuropathy can adversely affect function, oncologists and nurses typically do not have the skills needed to accurately assess and grade this toxicity. Performance data obtained by physical therapists who are expert in the evaluation of movement are needed to characterize the severity (grade), latency, and persistence of vincristine associated toxicity. This information will inform the timing and scope of subsequent screening and intervention trials.

Pathophysiology of Vincristine Toxicity

Vincristine, a vinca alkaloid, binds with tubulin and blocks polymerization into microtubules, resulting in arrest of mitosis in metaphase. This mechanism also affects axonal transport.[127] Structural changes in the cytoskeleton of large myelinated axons and accumulation of neurofilaments in dorsal sensory ganglion neurons have been documented in animal studies.[128] Reports also indicate that vincristine can unmask underlying hereditary neuropathies[129] and that a drug interaction between vincristine and antifungal azoles may exacerbate a mild neuropathy.[32,130-132] Animal and human studies indicate that the rate of vincristine clearance is associated with age, perhaps accounting for higher rates of vincristine neurotoxicity among adolescents and young adults.[133,134]

Vincristine Is Associated With both Acute and Long Term Neuropathy

Acute axonal peripheral neuropathy has been documented in children during ALL treatment and is likely associated with vincristine administration. This distal polyneuropathy can be initially uncomfortable, affecting both sensory and motor functions. Bed rest and immobility during neuropathy contribute to muscle wasting and can be accompanied by a loss in ankle and wrist dorsiflexion range of motion. Reinders-Messelink et al[135] reported mild deficits in vibratory perception, reduced amplitude of action potentials in median, ulnar and fibular sensory nerves, and mild muscle weakness in 11 children after receiving 8 doses of vincristine at 1.5 mg/m^2 per dose for remission induction and intensification therapy.

While some previous reports have dismissed this acute effect of chemotherapy as transient, recent findings indicate that many survivors have long-term neuropathy.[136] Harila-Saari et al [137]evaluated motor evoked

potentials (MEPs) in 32 children upon completing treatment for ALL and found prolonged latencies in both upper and lower extremity axons when responses were compared to an age, gender and height matched control group. Wright et al.[138] reported 10 degree differences in ankle dorsiflexion range of motion when they compared ALL survivors at least 1 year off therapy to age and gender matched normal controls. Harila-Saari et al[57] utilized somatosensory evoked potentials (SEP) to evaluate central and peripheral axonal integrity in 31 childhood ALL survivors who were at least 2 years off therapy. When compared to age and gender matched controls, median nerve stimulation in ALL survivors demonstrated prolonged SEP latencies at the level of the brachial plexus and spinal cord, as well as prolonged latencies at the level of spinal cord and cortex with tibial nerve stimulation at the knee. Lehtinen et al[139] showed that peripheral neuropathy persisted as long as 5 years off-therapy as measured by MEPs in 27 children treated for ALL.

Impact on Daily Life

Hand function is necessary for all aspects of daily life. Sensation, dexterity and strength are required for object manipulation during play, during eating, during dressing and bathing, and keyboarding and manipulating electronic devices as the child ages and eventually reaches adulthood and starts work. Hands are used to touch, to assist with communication and to help convey emotion. A child with a painful, insensate or weak hand will not be able to participate in day to day activities consistent with his or her role as a child.

Several studies have documented that peripheral neuropathy in children treated for ALL often manifests as handwriting problems. Reinders-Messelink et al[135] reported that ALL patients draw slower with longer pauses and increased drawing pressure. A separate report showed that handwriting difficulties persisted 2 years after completing therapy.[140] Handwriting is felt to be important by educators because it is essential to school success. Children spend 31% - 60% of their school hours in handwriting and other fine motor activities.[141] Even in the current computer age, difficulties can impede other higher order skills such as spelling, essay composition, note-taking, and expression of ideas.[142] Fine motor skills are needed for self-care skills such as dressing with buttons and zippers as well as using standard and small keyboards (e.g. calculator, cell phones).

Many ALL survivors report physical disability that adversely affects their daily life. Physical performance limitations were documented in 14.6% of adult ALL survivors in the Childhood Cancer Survivor Study cohort, impacting their ability to attend work or school and their participation in recreational physical activity.[143] Among adult survivors of ALL, only 42.9% self-report regular participation in physical activity compared to 51.3% of siblings ($p < 0.05$).[144] Small changes in muscular strength correspond to large change in function in other populations.[145]

Dose-Related Vincristine Toxicity

Previous investigators found no association between motor performance and vincristine dose among a heterogeneous sample of childhood cancer survivors.[146] However, we recently evaluated 321 adult survivors of childhood ALL treated with vincristine at St. Jude Children's Research Hospital and documented problems with ankle range of motion in 36.3%, sensation in 4.7%, vibration in 12.0%, deep tendon reflexes in 14.7% and ankle dorsiflexion strength in 21.2% of these young adults.[144] Ankle range of motion limitations were associated with reduced balance, mobility and ambulation skills in this 20+ year survivor population. After adjusting for both cranial radiation and methotrexate doses, total cumulative vincristine doses above 32 mg/m^2 were associated with ankle active dorsiflexion less than 5 degrees. Children enrolled on the standard regimen of the AR arm of AALL0932 are scheduled to receive 39 mg/m^2 (girls) to 57 mg/m^2 (boys).

Vincristine Toxicity is Amenable to Intervention

Early identification of children at risk for peripheral neuropathy is important because there are interventions to ameliorate physical impairments so that the child will not experience long term functional loss. Wright

et al [147] studied 40 children who received an individualized stretching and bracing program during treatment for ALL, measuring range of motion at multiple times during the course of disease therapy and then after therapy was completed. When compared to a historical control group, among whom 33% of age and sex-matched children with ALL had passive dorsiflexion range of motion less than 10 degrees, none of the children who participated in the individualized stretching and bracing program lost dorsiflexion range of motion.

Intervention is necessary because children with impaired motion and strength are at risk for injury and less than optimal participation in daily activities. Tabrizi et al[148] documented an association between frequent ankle injury and decreased ankle range of motion in healthy children. Full ankle range of motion is necessary for normal walking speed[149] and for complex upright tasks, like stair climbing[150] and participation in sports.[151-153]

Limitations with Current COG Resources

Currently, COG clinical trials only ascertain peripheral neuropathy outcomes in a limited fashion based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) categorization from assessment by pediatric oncology physicians. There are at least 2 major challenges in relying on CTCAE reporting. First, CTCAE categories are too broad and insensitive for clinically meaningful differences. Second, in clinical practice, physicians do not routinely ask about and test for peripheral neuropathy. Most physicians lack the expertise and time to accurately and comprehensively measure peripheral neuropathy. Therefore, physicians under-report the incidence and severity of chemotherapy associated peripheral neuropathy.[154,155] Neuropathy assessment is ideally done by a pediatric physical therapist trained in chemotherapy associated neuropathy. Most institutions do not have the resources to provide physical therapists at oncology clinic visits and COG per case reimbursement does not provide funds for this purpose. Thus, it would be impossible to conduct this research in the setting of the usual COG ALL protocols.

The CTCAE data are not adequate to inform clinical management of symptoms and the timing of interventions that can limit patients' participation in developmentally appropriate physical activity and learning. Critical data are needed regarding the timing, progression, and severity of peripheral neuropathy in ALL patients. The current study sample is particularly informative because we will have the data to compare the severity of neuropathy associated with monthly vs. every 3 month vincristine dosing. Because we will have high quality peripheral neuropathy data for both vincristine schedules, we will have sufficient data to plan future intervention studies to ameliorate functional outcomes regardless of which regimen moves forward in subsequent therapeutic studies.

Summary

Peripheral neuropathy is a toxicity that was previously under appreciated, and is only recently understood to impact long term functioning and quality of life in cancer patients. Children with ALL are at risk for both neurosensory and neuromotor impairments as a result of vincristine induced peripheral neuropathy. These impairments interfere with touch and vibration perception, ankle motion, ankle and hand strength, fine motor skill, balance and visual motor integration. In turn, these functional limitations impact normal movement (i.e. walking, running, jumping) and the normal developmental activities of childhood. Interventions are available to address these impairments, and if implemented early may ameliorate long term functional loss. Increased understanding of the pathophysiology causing these impairments is crucial to developing early intervention programs to prevent these deficits in the future.

The current practice of reporting peripheral neuropathy based on patient self-report and physician assessment through the CTCAE system results is too crude to accurately assess the incidence and severity of this toxicity and does not allow for accurate assessment of the effect of treatment interventions. Functional assessments by a trained physical therapist are needed to determine the timing, progression, and

severity of peripheral neuropathy in ALL patients. The selected tests are feasible, focused, and objective, but are too expensive to be funded by usual clinical trial consortium or cancer control resources. The current study will yield important data on the incidence, severity, and natural history of vincristine induced peripheral neuropathy in childhood ALL and is a critical first step needed in order to plan future intervention trials.

Knowledge of the onset and progression of peripheral neuropathy in children during treatment for ALL will inform screening guidelines and allow intervention to be implemented at the right time during the course of therapy. Early attention to small sensory and motor loss will prevent large losses in function as the child progresses through the course of therapy. Data from this study will also be informative for children at risk for vincristine associated neuropathy in other cancers. For example, treatment regimens for Wilm's tumor, rhabdomyosarcoma, and many central nervous system tumors include significant doses of vincristine that often lead to clinical neuropathies. This study thus represents a unique opportunity to understand the natural history of peripheral neuropathy in oncology patients.

16.2.2. Specific Aims and Hypotheses:
Specific Aim 1: To characterize the onset, severity, and natural history of vincristine-associated neuropathy by physical therapists in children undergoing therapy for Average Risk Acute Lymphoblastic Leukemia. We hypothesize the following:

Hypothesis 1: Children treated for Average Risk ALL will have clinically significant neurosensory impairments and functional loss at both 1) the end of consolidation therapy after 5 doses of vincristine, and 2) the end of Interim Maintenance II/Beginning of Maintenance immediately after receiving an additional 13 doses of vincristine over approximately 24 weeks.

Hypothesis 2: Children will have improved, but still sub-normal, neurosensory integrity and function during Maintenance therapy, as assessed 18 months after beginning the Maintenance phase of therapy.

Hypothesis 3: Children will not demonstrate complete recovery of neurosensory integrity and function 12 months after completing therapy.

Specific Aim 2: To compare the severity of vincristine associated neuropathy in children with Average Risk Acute Lymphoblastic Leukemia randomized to every 4 week vs. every 12 week vincristine therapy during Maintenance.

Hypothesis 4: Children randomized to every 4 week vincristine pulses during Maintenance will have more severe neurosensory impairments and functional losses than those randomized to every 12 week vincristine pulses.

16.3 Statistical Design

16.3.1 Analysis of Aim 1 to characterize the onset, severity, and natural history of vincristine-associated neuropathy by physical therapists in children undergoing therapy for Average Risk Acute Lymphoblastic Leukemia.

Because healthy children perform differently on tests of neuromotor performance based on their age, body weight, height, and sometimes sex, we will calculate for comparison, a set of expected mean values for each measure of performance (based on published normative data) that matches the distribution of our population. Strength in the ankle dorsiflexors is the primary outcome for the sample size calculations; we then calculate the minimal detectable difference for the other outcome measures based on the calculated sample size (displayed in Table 16.3.1.1 below). For example, a healthy 4 year old boy, on average, can generate 71 ± 22 Newtons of isometric force with his ankle dorsiflexors. A healthy 4 year old girl, on average can generate 75 ± 20 Newtons of force with her ankle dorsiflexors. If our population includes 70 boys and 60 girls who are all (hypothetically) 4 years of age, then our population comparison mean and standard deviation for dorsiflexion strength would be:

$$(70*71) + (60*75))/130 \pm ((70*22) + (60*20))/130 = 72.8 \pm 21.1 \text{ Newtons.}$$

This value will be compared at the first time point to our measured value with a 2 sample t-test using the formula:

$$\frac{x_1 - x_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

Using the ankle dorsiflexion strength measure as our primary outcome, with 130 children enrolled on the study and a 2-sided alpha level set at 0.0055 for the 9 different performance measures (0.05 divided by 9, Bonferroni adjustment), we have 90% power to detect 10.6 Newtons or a 0.5 standard deviation between the measured values and the expected values. At the second, third and fourth time points, the measured performance outcomes will be compared to expected performance outcomes (expected normative values will represent baseline time) using repeated measures analysis of variance (time as the dependent variable) in order to account for within participant correlation between measures.

Table 16.3.1.1 below demonstrates expected values and minimally detectable differences between expected and measured values on each of our performance measures. On the measures where a threshold of performance indicates an abnormality (sensation, vibration) the outcome is binomial. In those cases we will utilize a 2 sided binomial test to detect differences between the population expected and the measured proportions of children with ALL who have disordered function and generalized linear mixed models to allow for within person correlation when evaluating each outcome over time.

Table 16.3.1.1

Measure	Published Mean or Threshold for abnormality	Published Standard Deviation	Minimally detectable difference	Reference source
Mechanical pressure	1.36 Newton meters (log transformed)	0.35 Newton meters (log transformed)	0.18 Newton meters (log transformed)	156
Vibration	7.62 x/8	0.42 x/8	0.21 x/8	156
Handgrip strength	47.5 Newtons	12.3 Newtons	6.2 Newtons	157
Isometric ankle dorsiflexion strength	72.8 Newtons	21.1 Newtons	10.6 Newtons	158
Ankle dorsiflexion	18.1 degrees	6.9 degrees	3.5 degrees	150,159
Sit-ups and push-ups	6 repetitions 3 repetitions	3 repetitions 2 repetitions	1.5 repetitions 1 repetition	160
Purdue Pegboard	9.33 seconds	1.81 seconds	0.91 seconds	121
Six minute walk	519.2 Meters	92.9 Meters	46.5 Meters	161

To gain further insights regarding the burden of peripheral neuropathy, we plan to analyze associations between quality of life outcomes from the PedsQL and 1) participation in age appropriate activities on the PODCI, and 2) performance on the Purdue Pegboard and 6 Minute Walk.

16.3.2 Analysis of Aim 2 to compare the severity of vincristine associated neuropathy in children with Average Risk Acute Lymphoblastic Leukemia randomized to every 4 week vs. every 12 week vincristine therapy during Maintenance.

We will test the hypothesis that children randomized to every 4 week vincristine pulses during Maintenance will have more severe neurosensory impairments and functional losses than those randomized to every 12 week vincristine pulses. Both boys and girls will be evaluated and compared 18 months after starting maintenance. Differences in performance on between the two groups of patients on the tests of motor performance will also be evaluated with 2 sample t-tests. With 65 participants per group and a 2-sided alpha value of 0.0055 (allowing for multiple comparisons, we have 80% power to detect a 0.63 standard deviation difference between the 2 groups at the end of treatment.

16.3.3 Patient Accrual

We project that 75% of patients enrolled on the therapeutic study will be eligible and also enroll on the neuropathy study annually at select participating centers. The total annual accrual on the Average Risk ALL therapeutic study will be ~89 patients annually at the COG sites selected for the current ancillary neuropathy study based on past COG logs. Overall, we will enroll about 67 patients, estimated as 75% of 89 patients, per year at the participating sites. This corresponds to about 5 - 6 patients per month for a total of 24 months to meet our accrual goals.

16.4 **Significance**

Peripheral neuropathy is a toxicity that was previously under appreciated, but is now understood to impact long term functioning and quality of life in cancer patients. Children with ALL are at risk for both neurosensory and neuromotor impairments as a result of vincristine induced peripheral neuropathy. These impairments interfere with touch and vibration perception, ankle motion, ankle and hand strength, fine motor skill, balance and visual motor integration. These functional limitations impact daily activities and eventually, academic performance. Interventions are available to address these impairments, and if

implemented early may ameliorate long term functional loss. This project will generate needed data that could not be supported through the usual COG consortium mechanism.

An increased understanding of the pathophysiology causing these impairments is crucial to the design of future clinical trials that test early intervention programs designed to prevent and/or ameliorate these deficits. In addition, we will have the data to compare severity and progression of peripheral neuropathy between a vincristine schedule of every 4 weeks versus a vincristine schedule of every 12 weeks. This comparison would be useful to inform future clinical trials if event free survival does not differ between the 2 arms, but the incidence and severity of peripheral neuropathy is worse in one or the other arm. This may be particularly relevant because the therapeutic study is powered to detect a 3% difference between the treatment arms. Because we will have high quality peripheral neuropathy data for both vincristine schedules, we will have sufficient data to plan future intervention studies to ameliorate functional outcomes regardless of which regimen moves forward in subsequent therapeutic studies.

Generalizing beyond ALL, vincristine is used extensively in multiple other pediatric cancer conditions, including rhabdomyosarcoma, neuroblastoma, central nervous system tumors, and lymphoma. AALL0932 provides the opportunity to characterize the incidence and natural history of peripheral neuropathy in a population that is not confounded by administration of other drugs associated with peripheral neuropathy (e.g. cisplatinum) or nervous system deficits often present in patients with brain tumors. This population allows an opportunity to evaluate the potential contributions of vincristine toxicity to neurosensory outcomes in these other populations. Data from this study will thus inform other disease group monitoring or interventions in the future.

APPENDIX I: MERCAPTOPURINE DOSING GUIDELINES

MERCAPTOPURINE 75 mg/m²

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk
2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.17 – 2.21	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.22 – 2.26	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.27 – 2.30	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.31 – 2.35	3½ tab/ d x 7	1225 mg/wk
2.36 – 2.40	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk
2.41 – 2.45	3½ tab/ d x 5; 4 tab / d x 2	1275 mg/wk

2.46 – 2.49	3½ tab/ d x 4; 4 tab / d x 3	1300 mg/wk
2.50 – 2.54	4 tab/ d x 4; 3½ tab / d x 3	1325 mg/wk
2.55 – 2.59	4 tab/ d x 5; 3½ tab / d x 2	1350 mg/wk
2.60 – 2.64	4 tab/ d x 6; 3½ tab / d x 1	1375 mg/wk
2.65 – 2.69	4 tab/ d x 7	1400 mg/wk
2.70 – 2.73	4 tab/ d x 6; 4½ tab / d x 1	1425 mg/wk
2.74 – 2.78	4 tab/ d x 5; 4½ tab / d x 2	1450 mg/wk
2.79 – 2.83	4 tab/ d x 4; 4½ tab / d x 3	1475 mg/wk
2.84 – 2.88	4½ tab/ d x 4; 4 tab / d x 3	1500 mg/wk
2.89 – 2.92	4½ tab/ d x 5; 4 tab / d x 2	1525 mg/wk
2.93 – 2.97	4½ tab/ d x 6; 4 tab / d x 1	1550 mg/wk
2.98 – 3.00	4½ tab/ d x 7	1575 mg/wk

*****Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

APPENDIX II: THIOGUANINE DOSING GUIDELINES

THIOGUANINE 60 mg/m²

Body Surface Area (m²)*	Daily Dose (d) for 7 days (1 tablet = 40 mg)	Cumulative Weekly Dose
0.31 - 0.35	½ tab / d x 7	140 mg/wk
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.60 - 0.64	1 tab/ d x 6; ½ tab / d x 1	260 mg/wk
0.65 - 0.69	1 tab / day	280 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
0.79 - 0.83	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
0.98 - 1.02	1½ tab /day	420 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.31 - 1.35	2 tab / day	560 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
1.46 - 1.49	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
1.50 - 1.54	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
1.55 - 1.59	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
1.60 - 1.64	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
1.65 - 1.69	2½ tab / d	700 mg/wk
1.70 - 1.73	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
1.74 - 1.78	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
1.79 - 1.83	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
1.84 - 1.88	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
1.89 - 1.92	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
1.93 - 1.97	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk
1.98 - 2.02	3 tab / d x 7	840 mg/wk
2.03 - 2.07	3 tab / d x 6; 3½ tab / d x 1	860 mg/wk
2.08 - 2.11	3 tab / d x 5; 3½ tab / d x 2	880 mg/wk
2.12 - 2.16	3 tab / d x 4; 3½ tab / d x 3	900 mg/wk
2.17 - 2.21	3½ tab / d x 4; 3 tab / d x 3	920 mg/wk
2.22 - 2.26	3½ tab / d x 5; 3 tab / d x 2	940 mg/wk
2.27 – 2.30	3½ tab / d x 6; 3 tab / d x 1	960 mg/wk
2.31 – 2.35	3½ tab / d x 7	980 mg/wk

2.36 – 2.40	3½ tab / d x 6; 4 tab / d x 1	1000 mg/wk
2.41 – 2.45	3½ tab / d x 5; 4 tab / d x 2	1020 mg/wk
2.46 – 2.49	3½ tab / d x 4; 4 tab / d x 3	1040 mg/wk
2.50 – 2.54	4 tab / d x 4; 3½ tab / d x 3	1060 mg/wk
2.55 – 2.59	4 tab / d x 5; 3½ tab / d x 2	1080 mg/wk
2.60 – 2.64	4 tab / d x 6; 3½ tab / d x 1	1100 mg/wk
2.65 – 2.69	4 tab / d x 7	1120 mg/wk
2.70 – 2.73	4 tab / d x 6; 4½ tab / d x 1	1140 mg/wk
2.74 – 2.78	4 tab / d x 5; 4½ tab / d x 2	1160 mg/wk
2.79 – 2.83	4 tab / d x 4; 4½ tab / d x 3	1180 mg/wk
2.84 – 2.88	4½ tab / d x 4; 4 tab / d x 3	1200 mg/wk
2.89 – 2.92	4½ tab / d x 5; 4 tab / d x 2	1220 mg/wk
2.93 – 2.97	4½ tab / d x 6; 4 tab / d x 1	1240 mg/wk
2.98 – 3.00	4½ tab / d x 7	1260 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their TG doses calculated on actual BSA with no maximum dose.*

APPENDIX III: MERCAPTOPURINE DOSING GUIDELINES

MERCAPTOPURINE 50 mg/m²

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.33 - 0.39	½ tab / d x 5	125 mg/wk
0.40 - 0.46	½ tab / d x 6	150 mg/wk
0.47 - 0.53	½ tab / d x 7	175 mg/wk
0.54 - 0.60	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.61 - 0.67	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.68- 0.74	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.75 - 0.82	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.83 - 0.89	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.90 - 0.96	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.97 - 1.03	1 tab / d x 7	350 mg/wk
1.04 – 1.10	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
1.11 - 1.17	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
1.18 - 1.24	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
1.25 - 1.32	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.33 - 1.39	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.40 - 1.46	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.47 - 1.53	1½ tab / d x 7	525 mg/wk
1.54 - 1.60	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.61 - 1.67	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.68 - 1.74	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.75 - 1.82	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.83 - 1.89	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.90 - 1.96	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.97 - 2.03	2 tab / d x 7	700 mg/wk
2.04 – 2.10	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
2.11 – 2.17	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
2.18 – 2.24	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
2.25 – 2.32	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
2.33 – 2.39	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
2.40 – 2.46	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
2.47 – 2.53	2½ tab / d x 7	875 mg/wk
2.54 – 2.60	2½ tab / d x 6; 3 tab / d x 1	900 mg/wk

2.61 – 2.67	2½ tab / d x 5; 3 tab / d x 2	925 mg/wk
2.68 – 2.74	2½ tab / d x 4; 3 tab / d x 3	950 mg/wk
2.75 – 2.82	3 tab / d x 4; 2½ tab / d x 3	975 mg/wk
2.83 – 2.89	3 tab / d x 5; 2½ tab / d x 2	1000 mg/wk
2.90 – 2.96	3 tab / d x 6; 2½ tab / d x 1	1025 mg/wk
2.97 – 3.00	3 tab / d x 7	1050 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on*

APPENDIX IV: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY AALL0932
(for children from 7 through 12 years of age)

Standard Risk B-Lymphoblastic Leukemia

1 We have been talking with you about Acute Lymphoblastic Leukemia or ALL. ALL is a type of cancer that grows in the bone marrow. The bone marrow is inside your bones. It is where your blood is made. After doing tests, we have found that you have this type of cancer.

2 We are asking you to take part in a research study because you have Standard Risk ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat ALL and reduce the bad effects of the anticancer drugs. We will do this by trying different ways to treat ALL and seeing which one works better. We don't know which way is better. That is why we are doing this study.

3 Children who are part of this study will receive a treatment called chemotherapy. Chemotherapy is medicine that kills cancer. Children who are part of this study will get the usual treatment doctors use for ALL. Some of the children will get extra chemotherapy and some will get less chemotherapy. You will also have regular blood tests and several bone marrow tests and spinal taps during your treatment. These tests help doctors in deciding the most appropriate treatment for your ALL. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4 Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible, and with fewer bad effects; but we don't know for sure if there is any benefit of being part of this study.

5 Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. Steroid drugs, such as dexamethasone, are known causes of a disease called "osteonecrosis" (ON). Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones. Without blood, the bone tissue dies and causes the bone to breakdown. ON is most commonly seen in the hip joint. If the bones near a joint breakdown it can cause the joint to collapse. The exact reason why corticosteroids cause ON is not known. We hope that a reduced exposure to steroids such as dexamethasone will reduce the likelihood of some of the risks associated with treatment for ALL. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don't yet know about.

6 Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY AALL0932
(for children from 7 through 12 years of age)

Localized B-Lymphoblastic Lymphoma

1 We have been talking with you about localized B-lymphoblastic lymphoma or B-LLy. B-LLy is a type of cancer that can grow in the lymph system that is made up of lymph nodes and other tissue throughout the body, helping to fight infections and keep the body healthy. Lymph nodes are located all over your body. After doing tests, we have found that you have this type of cancer and it is only located in one particular area in the body.

2 We are asking you to take part in a research study because you have localized B-LLy. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat B-LLy and reduce the bad effects of the anticancer drugs. All patients with B-LLy on this study will receive the same treatment but we would like to learn more of how these patients are doing and whether we can find out which patients are doing better or worse. That is why we are doing this study.

3 Children who are part of this study will receive a treatment called chemotherapy. Chemotherapy is medicine that kills cancer. Children who are part of this study will get the treatment similar to that for children with B-ALL, a similar kind of cancer that affects the bone marrow. You will have regular blood tests, bone marrow tests, spinal taps and scans during your treatment. These tests help doctors in deciding the best treatment for your B-LLy. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4 Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible, and with fewer bad effects; but we don’t know for sure if there is any benefit of being part of this study.

5 Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are increased bad effects that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. Steroid drugs, such as dexamethasone, are known causes of a condition called “osteonecrosis” (ON). Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones. Without blood, the bone tissue dies and causes the bone to breakdown. ON is most commonly seen in the hip joint. The exact reason why corticosteroids cause ON is not known. We do not know for sure why these bad effects happen, which is why we are doing this study. Other things may happen to you that we don’t yet know about.

6 Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7 We are asking your permission to collect additional blood, as well as to use some tumor tissue to perform some special studies. These studies will help us better understand B-LLy. These samples would be taken when other standard tests are being performed. You can still be treated on this study even if you don't want to take part in these special studies.

INFORMATION SHEET REGARDING RESEARCH STUDY AALL0932
(for children from 13 through 17 years of age)

Localized B-Lymphoblastic Lymphoma

1 We have been talking with you about localized B-lymphoblastic lymphoma or B-LLy. B-LLy is a type of cancer that occurs in the lymph system, which is made up of the lymph nodes and other lymph tissue throughout the body. Lymph tissue makes and stores infection-fighting white blood cells called lymphocytes. These cells begin to grow in a disorderly fashion and no longer perform their usual function when a subject has lymphoma. After doing tests, we have found that you have this type of cancer and it is only located in a restricted area (localized).

2 We are asking you to take part in a research study because you have localized B-LLy. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat B-LLy and reduce the bad effects of the anticancer drugs. All patients with B-LLy on this study will receive the same treatment but we would like to learn more of how these patients are doing and whether we can find out which patients are doing better or worse. We do not know these things, which is why we are doing this study.

3 Children who are part of this study will receive a treatment called chemotherapy. Chemotherapy is medicine that kills cancer. Children who are part of this study will get the same treatment given to children with B-ALL (a similar kind of cancer that affects the bone marrow), but with one difference during the phase of therapy called Maintenance - you will have the same duration of Maintenance therapy whether you are male or female, unlike Maintenance for B-ALL, where male patients get treatment for longer. If you have Down syndrome and B-LLy (DS B-LLy), you will get exactly the same treatment given to patients with DS B-ALL. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. You will also have scans performed to make sure the B-LLy is responding to treatment. These tests help doctors in deciding the most appropriate treatment for your B-LLy. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4 Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible, and with fewer bad effects; but we don’t know for sure if there is any benefit of being part of this study.

5 Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. Steroid drugs, such as dexamethasone, are known causes of a disease called “osteonecrosis” (ON). Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones. Without blood, the bone tissue dies and causes the bone to breakdown. ON is most commonly seen in the hip joint. If the bones near a joint breakdown it can cause the joint to collapse. The exact reason why corticosteroids cause ON is not known. We do not know for sure why these toxicities and side effects occur, which is why we are doing this study. Other things may happen to you that we don’t yet know about.

6 Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7 We are asking your permission to collect additional blood, as well as to use some left over tumor tissue to perform some special studies. These studies will help us better understand B-LLy. Some of the studies involve studying the lymphoma cells using special tests to help us understand better, why some patients may responds differently to treatment given for lymphoma. These samples would be taken when other standard tests are being done, so there will be no extra procedures performed. You can still be treated on this study even if you don't want to take part in these special studies.

APPENDIX V: STAGING CLASSIFICATION OF CHILDHOOD NON-HODGKIN LYMPHOMA

Modified from Murphy [Seminars in Oncology (1980) 7; 332-339]

Stage	Criteria for extent of disease
Localized	
I	A single tumour (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
II	A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tumour, usually in the ileocaecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected
Disseminated	
III	Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All primary intra-thoracic tumours (mediastinal, pleural, thymic) All extensive primary intra-abdominal disease. All paraspinal or epidural tumours, regardless of other tumour site(s).
IV	Any of the above with initial CNS and/or bone marrow involvement.

Enumeration of Number of Regions of Nodal Involvement

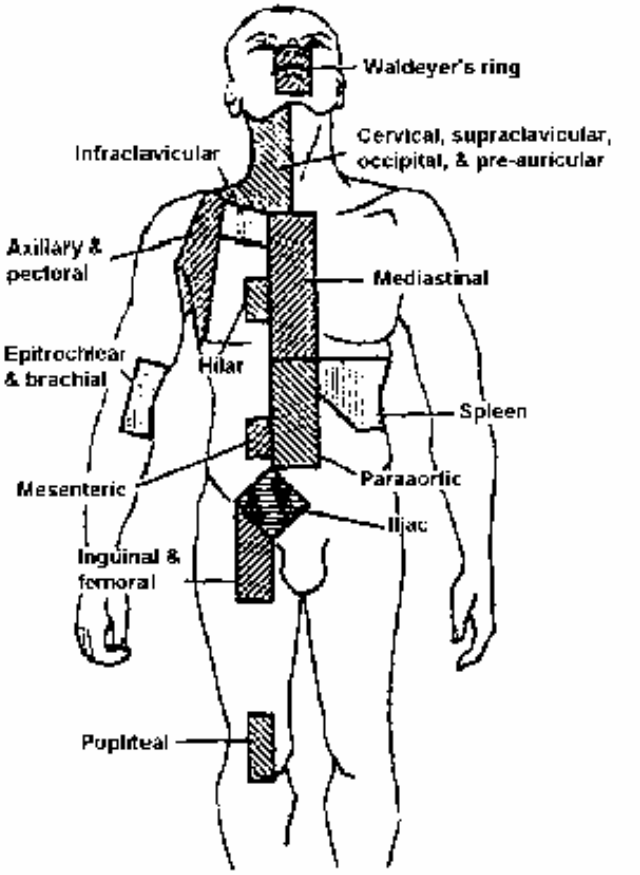
Each of these twenty regions is counted separately for purposes of determining number of sites of involvement.

Peripheral Regions

Right neck; cervical, supraclavicular, occipital, and pre-auricular
Left neck; cervical, supraclavicular, occipital, and pre-auricular
Right infraclavicular
Left infraclavicular
Right axilla and pectoral
Left axilla and pectoral
Right epitrochlear and brachial
Left epitrochlear and brachial

Central Regions
- Waldeyer's ring (including base of tongue)
- Mediastinum (including paratracheal)
- Hilar
- Mesenteric
- Paraaortic (including retrocrural, portal and celiac)
- Splenic/splenic hilar

Lower Regions
- Right iliac
- Left iliac
- Right inguinal and femoral
- Left inguinal and femoral
- Right popliteal
- Left popliteal



Anatomical Regions for the Staging Lymphoma

Clinical criteria for nodal involvement - upper torso

Above the diaphragm, the following will be considered positive for lymphoma, provided they are not obviously infected.

- Any cervical or axillary node >3 cm^3 on physical examination, ultrasound, CT or MRI scan.
- Any cluster of matted or adherent nodes.
- Any enlarged supraclavicular nodes.
- Any mediastinal adenopathy
- Any Gallium-positive nodes

Clinical Criteria for Nodal Involvement - lower torso

Below the diaphragm, the following areas of involvement will be considered positive for lymphoma unless they are pathologically proven to be negative.

- Any node >2 cm^3 on CT scan or ultrasound.
- Any Gallium-positive nodes, liver or spleen.
- A spleen or liver that has focal defects on CT or ultrasound or MRI

APPENDIX VI: CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

APPENDIX VII: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

Cyclophosphamide

Drugs that may interact with cyclophosphamide*
• Allopurinol • Chloramphenicol • Cyclosporine • Digoxin • Etanercept • Hydrochlorothiazide • Indomethacin • Nevirapine • Pentostatin • Warfarin

Food and supplements that may interact with cyclophosphamide**
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Cytarabine (by vein)

Drugs that may interact with cytarabine*
• Clozapine, digoxin, flucytosine, leflunomide

Food and supplements that may interact with cytarabine**
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Dexamethasone

Drugs that may interact with dexamethasone*

• Antibiotics
  ○ Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine
• Antifungals
  ○ Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  ○ Leflunomide, tofacitinib
• Anti-rejection medications

- Cyclosporine, sirolimus, tacrolimus
- Antiretrovirals and antivirals
  - Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
- Anti-seizure medications
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Heart medications
  - Amiodarone, amlodipine, dronedenarone, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Some oral contraceptives or birth control medications
- Many other drugs, including the following:
  - Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Doxorubicin

Drugs that may interact with doxorubicin*
• Some antiepileptics (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (stavudine, zidovudine) • Other agents, such as clozapine, cyclosporine, verapamil, and warfarin

Food and supplements that may interact with doxorubicin**
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Leucovorin

Drugs that may interact with leucovorin*
• Some antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone)

Food and supplements that may interact with leucovorin**
• Folic acid

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Mercaptopurine

Drugs that may interact with mercaptopurine*
• Artiritis medications: leflunomide, tofacitinib • Other medications, such as allopurinol, azathioprine, clozapine, febuxostat, natalizumab, olsalazine, sulfasalazine, warfarin

Food and supplements that may interact with mercaptopurine**
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Methotrexate (by mouth or by vein)

Drugs that may interact with methotrexate*
• Some antibiotics (amoxicillin, Bactrim, chloramphenicol, ciprofloxacin, penicillin, piperacillin, tetracycline) • Some anti-inflammatory drugs (aspirin, acetaminophen, ibuprofen, naproxen, ketorolac) • Some heartburn medications (esomeprazole, lansoprazole, omeprazole, pantoprazole) • Several other specific agents, including the following: amiodarone, clozapine, cyclosporine, eltrombopag, leflunomide, phenytoin, pimecrolimus, probenecid, pyrimethamine, retinoids, theophylline, warfain

Food and supplements that may interact with methotrexate**
• Alcohol • Echinacea • Some vitamins, including those that contain folic acid or high doses of vitamin C

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Pegaspargase

Drugs that may interact with pegaspargase*
• Leflunomide, natalizumab, tofacitinib

Food and supplements that may interact with pegaspargase**
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Thioguanine

Drugs that may interact with thioguanine*
• Arthritis medications: leflunomide, tofacitinib • Other medications, such as allopurinol, clozapine, natalizumab, olsalazine, sulfasalazine

Food and supplements that may interact with thioguanine**
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Vincristine

Drugs that may interact with vincristine*

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Aripiprazole, nefazodone, trazodone
• Antifungals
  ○ Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  ○ Leflunomide, tocilizumab, tofacitinib
• Anti-rejection medications
  ○ Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  ○ Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir
• Anti-seizure medications
  ○ Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  ○ Amiodarone, digoxin, dronedenarone, propranolol, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  ○ Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin

Food and supplements that may interact with vincristine**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

REFERENCES:

1. Schultz KR, Pullen DJ, Sather HN, et al: Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). Blood 109(3):926-935, 2007
2. Borowitz MJ, Devidas M, Hunger SP, et al: Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood 111(12):5477-5485, 2008
3. Matloub Y, Bostrom BC, Hunger SP, et al: Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. Blood 118:243-51, 2011
4. Balis FM, Holcenberg JS, Poplack DG, et al: Pharmacokinetics and pharmacodynamics of oral methotrexate and mercaptopurine in children with lower risk acute lymphoblastic leukemia: a joint children's cancer group and pediatric oncology branch study. Blood 92:3569-77, 1998
5. Balis FM, Savitch JL, Bleyer WA: Pharmacokinetics of oral methotrexate in children. Cancer Res 43:2342-5, 1983
6. Bleyer WA: The clinical pharmacology of methotrexate: new applications of an old drug. Cancer 41:36-51, 1978
7. Teresi ME, Crom WR, Choi KE, et al: Methotrexate bioavailability after oral and intramuscular administration in children. J Pediatr 110:788-92, 1987
8. Balis FM, Lester CM, Chrousos GP, et al: Differences in cerebrospinal fluid penetration of corticosteroids: possible relationship to the prevention of meningeal leukemia. J Clin Oncol 5:202-7, 1987
9. Dervieux T, Hancock M, Evans W, et al: Effect of methotrexate polyglutamates on thioguanine nucleotide concentrations during continuation therapy of acute lymphoblastic leukemia with mercaptopurine. Leukemia 16:209-12, 2002
10. Pui CH, Relling MV, Sandlund JT, et al: Rationale and design of Total Therapy Study XV for newly diagnosed childhood acute lymphoblastic leukemia. Ann Hematol 83 Suppl 1:S124-6, 2004
11. Winick N, Shuster JJ, Bowman WP, et al: Intensive oral methotrexate protects against lymphoid marrow relapse in childhood B-precursor acute lymphoblastic leukemia. J Clin Oncol 14:2803-11, 1996
12. Relling MV, Hancock ML, Boyett JM, et al: Prognostic importance of 6-mercaptopurine dose intensity in acute lymphoblastic leukemia. Blood 93:2817-23, 1999
13. Relling MV, Hancock ML, Boyett JM, et al: Prognostic importance of 6-mercaptopurine dose intensity in acute lymphoblastic leukemia. Blood 93:2817-23, 1999
14. Chessells JM, Leiper AD, Tiedemann K, et al: Oral methotrexate is as effective as intramuscular in maintenance therapy of acute lymphoblastic leukaemia. Arch Dis Child 62:172-6, 1987
15. Stocco G, Cheok MH, Crews KR, et al: Genetic polymorphism of inosine triphosphate pyrophosphatase is a determinant of mercaptopurine metabolism and toxicity during treatment for acute lymphoblastic leukemia. Clin Pharmacol Ther 85(2):164-72, 2009
16. McLeod HL, Krynetski EY, Relling MV, et al: Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. Leukemia 14(4):567-572, 2000
17. Relling MV, Hancock ML, Rivera GK, et al: Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus. J Natl Cancer Inst 91:2001-8, 1999
18. Hockenberry M, Krull K, Moore K, et al: Longitudinal evaluation of fine motor skills in children with leukemia. J Pediatr Hematol Oncol 29(8):535-539, 2007
19. Walsh D, Avashia J: Glucocorticoids in clinical oncology. Cleve Clin J Med 59(5):505-515, 1992
20. Sioka C, Kyritsis AP: Central and peripheral nervous system toxicity of common chemotherapeutic agents. Cancer Chemother Pharmacol 63(5):761-767, 2009

21. Bleyer WA, Sather HN, Nickerson HJ, et al: Monthly pulses of vincristine and prednisone prevent bone marrow and testicular relapse in low-risk childhood acute lymphoblastic leukemia: a report of the CCG-161 study by the Childrens Cancer Study Group. J Clin Oncol 9:1012-21, 1991
22. Richards S: Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children. Childhood ALL Collaborative Group. Lancet 347(9018):1783-8, 1996
23. Lange BJ, Bostrom BC, Cherlow JM, et al: Double-delayed intensification improves event-free survival for children with intermediate-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Blood 99:825-33, 2002
24. Conter V, Valsecchi MG, Silvestri D, et al: Pulses of vincristine and dexamethasone in addition to intensive chemotherapy for children with intermediate-risk acute lymphoblastic leukaemia: a multicentre randomised trial. Lancet 369:123-31, 2007
25. De Moerloose B, Suciu S, Bertrand Y, et al: Improved Outcome with Pulses of Vincristine and Steroids in Continuation Therapy of Children with Average Risk Acute Lymphoblastic Leukemia (ALL) and Non Hodgkin Lymphoma (NHL): Final Report of the EORTC Randomized Phase III Trial 58951. ASH Annual Meeting Abstracts 112(11):11, 2008
26. Buchanan N, Maloney K, Tsang S, et al: Risk of depression, anxiety, and somatization one month after diagnosis in children with standard risk ALL on COG AALL0331. . J Clin Oncol (Meeting Abstracts) 26(15_suppl):10052, 2008
27. Forsyth B: Early Health Crises and Vulnerable Children. In: Carey W, Crocker A, Coleman W, et al., editors. Developmental-Behavioral Pediatrics. Philadelphia: Saunders Elsevier, 2009
28. Daltroy LH, Liang MH, Fossel AH, et al: The POSNA pediatric musculoskeletal functional health questionnaire: report on reliability, validity, and sensitivity to change. Pediatric Outcomes Instrument Development Group. Pediatric Orthopaedic Society of North America. J Pediatr Orthop 18:561-71, 1998
29. Reynolds CR, & Kamphaus, R. W: *BASC-2: Behavior Assessment System for Children, Second Edition*. Circle Pines, MN, AGS Publishing, 2004
30. Limburg H, Shaw AK, McBride ML: Impact of childhood cancer on parental employment and sources of income: a Canadian pilot study. Pediatr Blood Cancer 51(1):93-98, 2008
31. Stevens B, Croxford R, McKeever P, et al: Hospital and home chemotherapy for children with leukemia: a randomized cross-over study. Pediatr Blood Cancer 47(3):285-292, 2006
32. Postma TJ, Benard BA, Huijgens PC, et al: Long-term effects of vincristine on the peripheral nervous system. J Neurooncol 15(1):23-27, 1993
33. Hudson MM, Rai SN, Nunez C, et al: Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. J Clin Oncol 25(24):3635-3643, 2007
34. Lipshultz SE, Lipsitz SR, Sallan SE, et al: Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 23(12):2629-2636, 2005
35. Sorensen K, Levitt G, Bull C, et al: Anthracycline dose in childhood acute lymphoblastic leukemia: issues of early survival versus late cardiotoxicity. J Clin Oncol 15(1):61-68, 1997
36. MatloubY, Bruce C. Bostrom, Anne L Angiolillo, et al: Children with NCI Standard Risk Acute Lymphoblastic Leukemia (ALL) and TEL-AML1 or Favorable Chromosome Trisomies Are Almost Certain to Be Cured with Graduated Intensity Therapy: Results of the CCG - 1991 Study. Blood (ASH Annual Meeting Abstracts) Abstract 320, 2009
37. Whitlock JA: Down syndrome and acute lymphoblastic leukaemia. Br J Haematol 135(5):595-602, 2006
38. Maloney K: Improvement in the Infection-related Mortality for Children with Down Syndrome (DS) in Contemporary Children's Oncology Group (COG) Acute Lymphoblastic Leukemia (ALL) Clinical Trials. American Society of Pediatric Hematology/Oncology:1596, 2008
39. Garre ML, Relling MV, Kalwinsky D, et al: Pharmacokinetics and toxicity of methotrexate in children with Down syndrome and acute lymphocytic leukemia. J Pediatr 111(4):606-612, 1987

40. Taub JW GY: Down syndrome, drug metabolism and chromosome 21. Pediatr Blood Cancer 44(1):33-9, 2005
41. Moorman AV, Ensor HM, Richards SM, et al: Prognostic effect of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: results from the UK Medical Research Council ALL97/99 randomised trial. Lancet Oncol 11:429-38, 2010
42. Attarbaschi A, Mann G, Panzer-Grumayer R, et al: Minimal residual disease values discriminate between low and high relapse risk in children with B-cell precursor acute lymphoblastic leukemia and an intrachromosomal amplification of chromosome 21: the Austrian and German acute lymphoblastic leukemia Berlin-Frankfurt-Munster (ALL-BFM) trials. J Clin Oncol 26:3046-50, 2008
43. Moorman AV, Richards SM, Robinson HM, et al: Prognosis of children with acute lymphoblastic leukemia (ALL) and intrachromosomal amplification of chromosome 21 (iAMP21). Blood 109:2327-30, 2007
44. Burkhardt B, Reiter A, Landmann E, et al: Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the berlin-frankfurt-muenster group. J Clin Oncol 27:3363-9, 2009
45. Ducassou S, Ferlay C, Bergeron C, et al: Clinical presentation, evolution, and prognosis of precursor B-cell lymphoblastic lymphoma in trials LMT96, EORTC 58881, and EORTC 58951. Br J Haematol 152:441-51, 2011
46. Bostrom BC, Sensel MR, Sather HN, et al: Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Blood 101:3809-17, 2003
47. Mitchell CD, Richards SM, Kinsey SE, et al: Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. Br J Haematol 129:734-45, 2005
48. Teuffel O, Kuster SP, Hunger SP, et al: Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. Leukemia 25:1232-8, 2011
49. Stark B, Avigad S, Luria D, et al: Bone marrow minimal disseminated disease (MDD) and minimal residual disease (MRD) in childhood T-cell lymphoblastic lymphoma stage III, detected by flow cytometry (FC) and real-time quantitative polymerase chain reaction (RQ-PCR). Pediatr Blood Cancer 52:20-5, 2009
50. Duval M, Suciu S, Ferster A, et al: Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. Blood 99:2734-9, 2002
51. Silverman LB, Levy DE, Dalton VK, et al: Outcome of Dana-Farber cancer institute (DFCI) consortium protocol 95-01 for children with newly diagnosed acute lymphoblastic leukemia (ALL). ASH Annual Meeting Abstracts 104(11):679, 2004
52. Silverman LB, Gelber RD, Dalton VK, et al: Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood 97:1211-1218, 2001
53. Asselin BL, Whitin JC, Coppola DJ, et al: Comparative pharmacokinetic studies of three asparaginase preparations. J Clin Oncol. 11(9):1780-6, 1993
54. Brenner DE, Wiernik PH, Wesley M, et al: Acute doxorubicin toxicity. Relationship to pretreatment liver function, response, and pharmacokinetics in patients with acute nonlymphocytic leukemia. Cancer 53:1042-1048, 1984
55. Langer T, Martus P, Ottensmeier H, et al: CNS late-effects after ALL therapy in childhood. Part III: neuropsychological performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. Med Pediatr Oncol 38(5):320-8, 2002

56. Mulhern RK, Palmer SL: Neurocognitive late effects in pediatric cancer. Curr Probl Cancer 27(4):177-97, 2003
57. Harila-Saari AH, Paakko EL, Vainionpaa LK, et al: A longitudinal magnetic resonance imaging study of the brain in survivors in childhood acute lymphoblastic leukemia. Cancer 83(12):2608-17, 1998
58. Asato R, Akiyama Y, Ito M, et al: Nuclear magnetic resonance abnormalities of the cerebral white matter in children with acute lymphoblastic leukemia and malignant lymphoma during and after central nervous system prophylactic treatment with intrathecal methotrexate. Cancer 70(7):1997-2004, 1992
59. Iuvone L, Mariotti P, Colosimo C, et al: Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. Cancer 95(12):2562-70, 2002
60. Paakko E, Vainionpaa L, Pyhtinen J, et al: Minor changes on cranial MRI during treatment in children with acute lymphoblastic leukaemia. Neuroradiology 38(3):264-8, 1996
61. Biti GP, Magrini SM, Villari N, et al: Brain damage after treatment for acute lymphoblastic leukemia. A report on 34 patients with special regard to MRI findings. Acta Oncol. 28(2):253-6, 1989
62. Wilson DA, Nitschke R, Bowman ME, et al: Transient white matter changes on MR images in children undergoing chemotherapy for acute lymphocytic leukemia: correlation with neuropsychologic deficiencies. Radiology 180(1):205-9, 1991
63. Schrappe M, Reiter A, Ludwig WD, et al: Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss ALL-BFM Study Group. Blood 95(11):3310-22, 2000
64. Brouwers P, Riccardi R, Fedio P, et al: Long-term neuropsychologic sequelae of childhood leukemia: correlation with CT brain scan abnormalities. J Pediatr 106(5):723-8, 1985
65. Rollins N, Winick N, Bash R, et al: Acute methotrexate neurotoxicity: findings on diffusion-weighted imaging and correlation with clinical outcome. AJNR Am J Neuroradiol 25(10):1688-95, 2004
66. Laitt RD, Chambers EJ, Goddard PR, et al: Magnetic resonance imaging and magnetic resonance angiography in long term survivors of acute lymphoblastic leukemia treated with cranial irradiation. Cancer 76(10):1846-52, 1995
67. Kramer JH, Norman D, Brant-Zawadzki M, et al: Absence of white matter changes on magnetic resonance imaging in children treated with CNS prophylaxis therapy for leukemia. Cancer 61(5):928-30, 1988
68. Winick NJ, Bowman WP, Kamen BA, et al: Unexpected acute neurologic toxicity in the treatment of children with acute lymphoblastic leukemia. J Natl Cancer Inst 84(4):252-6, 1992
69. Bleyer WA: Neurologic sequelae of methotrexate and ionizing radiation: a new classification. Cancer Treat Rep 65 suppl 65 Suppl1:89-98, 1981
70. Meadows AT, Gordon J, Massari DJ, et al: Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. Lancet 2(8254):1015-8, 1981
71. Mulhern RK, Fairclough D, Ochs J: A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy, or no cranial irradiation. J Clin Oncol. 9(8):1348-56, 1991
72. Williams JM, Ochs J, Davis KS, et al: The subacute effects of CNS prophylaxis for acute lymphoblastic leukemia on neuropsychological performance: a comparison of four protocols. Arch Clin Neuropsychol. 1(2):183-92, 1986
73. Steinberg GK, Kunis D, DeLaPaz R, et al: Neuroprotection following focal cerebral ischaemia with the NMDA antagonist dextromethorphan, has a favourable dose response profile. Neurol Res. 15(3):174-80, 1993

74. Steinberg GK, Bell TE, Yenari MA: Dose escalation safety and tolerance study of the N-methyl-D-aspartate antagonist dextromethorphan in neurosurgery patients. J Neurosurg 84(5):860-6, 1996
75. Blin O, Azulay JP, Desnuelle C, et al: A controlled one-year trial of dextromethorphan in amyotrophic lateral sclerosis. Clin Neuropharmacol 19(2):189-92, 1996
76. Gredal O, Werdelin L, Bak S, et al: A clinical trial of dextromethorphan in amyotrophic lateral sclerosis. Acta Neurol Scand 96(1):8-13, 1997
77. Hollander D, Pradas J, Kaplan R, et al: High-dose dextromethorphan in amyotrophic lateral sclerosis: phase I safety and pharmacokinetic studies. Ann Neurol 36(6):920-4, 1994
78. Wiedemann BC, Balis FM, Murphy RF, et al: Carboxipepetidase-G2, thymidyne, and leucovorin rescue in cancer patients with mehtotrexate-induced renal dysfunction. J Cin Oncol-induced renal dysfunction 15(5):2125-34, 1997
79. DeAngelis LM, Tong WP, Lin S, et al: Carboxipeptidase G2 rescue after high-dose methostrexate. J Cin Oncol-induced renal dysfunction 14(7):2145-9, 1996
80. Weinshilboum RM, Sladek SL: Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. Am.J.Hum.Genet 32:651-662, 1980
81. Bostrom B, Erdmann G: Cellular pharmacology of 6-mercaptopurine in acute lymphoblastic leukemia. Am.J.Pediatr.Hematol.Oncol. 15:80-86, 1993
82. Weinshilboum RM: Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase. Drug Metab Dispos 29:601-605, 2001
83. Lennard L, Lewis IJ, Michelagnoli M, et al: Thiopurine methyltransferase deficiency in childhood lymphoblastic leukaemia: 6-mercaptopurine dosage strategies. Med.Pediatr.Oncol. 29:252-255, 1997
84. Yates CR, Krynetski EY, Loennechen T, et al: Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. Ann.Intern.Med 126:608-614, 1997
85. Otterness D, Szumlanski C, Lennard L, et al: Human thiopurine methyltransferase pharmacogenetics: gene sequence polymorphisms. Clin.Pharmacol.Ther 62:60-73, 1997
86. Hon YY, Fessing MY, Pui C-H, et al: Polymorphism of the thiopurine S-methyltransferase gene in African Americans. Hum.Mol.Genet 8:371-376, 1999
87. Krynetski EY, Evans WE: Genetic polymorphism of thiopurine S-methyltransferase: molecular mechanisms and clinical importance. Pharmacology 61:136-146, 2000
88. Microtubule-Targeting Agents, The Chemotherapy Source Book, Perry, MC (ed.), Publisher: Williams and Wilkins, Baltimore, MD, 387-425 (391). 2nd edition.
89. Van den Berg HW, Desai ZR, Wilson R, et al: The pharmacokinetics of vincristine in man: reduced drug clearance associated with raised serum alkaline phosphatase and dose-limited elimination. Cancer Chemother Pharmacol 8 (2):215-219, 1982
90. Relling MV, Pui CH, Sandlund JT, et al: Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. Lancet 356:285-290, 2000
91. Pui CH, Howard SC: Current management and challenges of malignant disease in the CNS in paediatric leukaemia. Lancet Oncol, 2008
92. Bucaneve G, Micozzi A, Menichetti F, et al: Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 353:977-87, 2005
93. Gafter-Gvili A, Fraser A, Paul M, et al: Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 142:979-95, 2005
94. Freidlin B, Korn EL: A comment on futility monitoring. Control Clin Trials 23:355-66, 2002
95. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-86, 2007
96. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 17:1244, 1999

97. Swerdlow SH, Campo E, Harris NL, et al: WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. IARC: Lyon., 2008
98. Varni JW, Burwinkle TM, Seid M, et al: The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 3(6):329-341, 2003
99. Epstein N, Baldwin L, Bishop D: The McMaster Family Assessment Device. Journal of Marital & Family Therapy 9:171-180, 1983
100. Miller I, Epstein N, Bishop D, et al: The McMaster Family Assessment Device: Reliability and validity. Journal of Marital & Family Therapy 11:345-356, 1985
101. Miller I, Ryan C, Keitner G, et al: The McMaster approach to families: Theory, assessment, treatment and research. Journal of Family Therapy 22:168-189, 2000
102. Kabacoff RI, Miller IW, Bishop DS, et al: A psychometric study of the McMaster Family Assessment Device in psychiatric, medical, and nonclinical samples. Journal of Family Psychology 3:431-439, 1990
103. Forsyth BW, Horwitz SM, Leventhal JM, et al: The child vulnerability scale: an instrument to measure parental perceptions of child vulnerability. J Pediatr Psychol 21(1):89-101, 1996
104. Thomasgard M, Metz WP: The vulnerable child syndrome revisited. J Dev Behav Pediatr 16(1):47-53, 1995
105. Drigan R, Spirito A, Gelber RD: Behavioral effects of corticosteroids in children with acute lymphoblastic leukemia. Med Pediatr Oncol 20(1):13-21, 1992
106. Cairns NU, Klopovich P, Hearne E, et al: School attendance of children with cancer. J Sch Health 52:152-5, 1982
107. Lansky S, Cairns N, Zwarnes W: School attendance among children with cancer: A report from two centers. J Psychosoc Oncol 1:75, 1983
108. Stehbens JA, Kisker CT, Wilson BK: School behavior and attendance during the first year of treatment for childhood cancer. Psychology in the Schools 20:223-228, 1983
109. Spielberger CD, Gorusch RL, Lushene RE: Manual for the State-Trait Anxiety Inventory. Palo Alto: CA, Consulting Psychologists Press. 1970
110. Katz ER: Illness impact and social reintegration, in Kellerman J (ed): Psychological aspects of cancer in children. Springfield, IL, Thomas, .197-209, 1980
111. Madan-Swain A, Austin H, Taylor-Cook P: Returning to school after a serious illness or injury, in Brown RT (ed): Cognitive aspects of chronic illness in children. New York, NY, Guilford Press:312-332, 1999
112. Earle E, Clarke S, Eiser C, et al: Building a new normality': Mothers' experience of caring for a child with acute lymphoblastic leukemia. Child: care, health and development. 33:155-160, 2006
113. Estroff DB, Yando R, Burke K, et al: Perceptions of preschoolers' vulnerability by mothers who had delivered preterm. J Pediatr Psychol 19:709-21, 1994
114. Anthony KK, Gil KM, Schanberg LE: Brief report: Parental perceptions of child vulnerability in children with chronic illness. J Pediatr Psychol 28:185-90, 2003
115. Dockerty JD, Skegg DC, Williams SM: Economic effects of childhood cancer on families. J Paediatr Child Health 39(4):254-258, 2003
116. Eiser C, Upton P: Costs of caring for a child with cancer: a questionnaire survey. Child Care Health Dev 33(4):455-459, 2007
117. Lansky SB, Cairns NU, Clark GM, et al: Childhood cancer: nonmedical costs of the illness. Cancer 43(1):403-408, 1979
118. Moore DS: The Basic Practice of Statistics. New York, W. H. Freeman and Company, 1995
119. Conover WJ: Practical Nonparametric Statistics (ed Third). New York, John Wiley & Sons, Inc., 1999
120. Buizer AI, de Sonneville LM, Veerman AJ: Effects of chemotherapy on neurocognitive function in children with acute lymphoblastic leukemia: a critical review of the literature. Pediatr Blood Cancer 52(4):447-54, 2009

121. Wilson BC, Iacoviello JM, Wilson JJ, et al: Purdue Pegboard performance of normal preschool children. J Clin Neuropsychol 4:19-26, 1982
122. Saleh FG, Seidman RJ: Drug-induced myopathy and neuropathy. J Clin Neuromuscul Dis 5:81-92, 2003
123. Malik B, Stillman M: Chemotherapy-induced peripheral neuropathy. Curr Pain Headache Rep 12:165-74, 2008
124. Gilchrist L, Tanner L, al. e: Measuring chemotherapy-induced peripheral neuropathy in children: development of the Ped-mTNS and pilot study results. Rehabilitation Oncology 27(3):7-15, 2009
125. Winter C, Muller C, Hoffmann C, et al: Physical activity and childhood cancer. Pediatr Blood Cancer, 2009
126. Vainionpaa L: Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. Eur J Pediatr 152(2):115-119, 1993
127. Peltier AC, Russell JW: Recent advances in drug-induced neuropathies. Curr Opin Neurol 15:633-8, 2002
128. Topp KS, Tanner KD, Levine JD: Damage to the cytoskeleton of large diameter sensory neurons and myelinated axons in vincristine-induced painful peripheral neuropathy in the rat. J Comp Neurol 424:563-76, 2000
129. Mercuri E, Poulton J, Buck J, et al: Vincristine treatment revealing asymptomatic hereditary motor sensory neuropathy type 1A. Arch Dis Child 81:442-3, 1999
130. Bohme A, Ganser A, Hoelzer D: Aggravation of vincristine-induced neurotoxicity by itraconazole in the treatment of adult ALL. Ann Hematol 71:311-2, 1995
131. Bermudez M, Fuster JL, Llinares E, et al: Itraconazole-related increased vincristine neurotoxicity: case report and review of literature. Journal: J Pediatr Hematol Oncol. (27):389-92, 2005
132. Mantadakis E, Amoiridis G, Kondi A, et al: Possible increase of the neurotoxicity of vincristine by the concurrent use of posaconazole in a young adult with leukemia. J Pediatr Hematol Oncol 29:130, 2007
133. Crom WR, de Graaf SS, Synold T, et al: Pharmacokinetics of vincristine in children and adolescents with acute lymphocytic leukemia. J Pediatr 125:642-9, 1994
134. Dambska M, Muzylak M, Maslinska D: The features of peripheral nerve lesions in young and adult rabbits after vincristine administration. Folia Neuropathol 33:21-4, 1995
135. Reinders-Messelink HA, Van Weerden TW, Fock JM, et al: Mild axonal neuropathy of children during treatment for acute lymphoblastic leukaemia. Eur J Paediatr Neurol 4:225-33, 2000
136. Legha SS: Vincristine neurotoxicity. Pathophysiology and management. Med Toxicol 1:421-7, 1986
137. Harila-Saari AH, Huuskonen UE, Tolonen U, et al: Motor nervous pathway function is impaired after treatment of childhood acute lymphoblastic leukemia: a study with motor evoked potentials. Med Pediatr Oncol 36:345-51, 2001
138. Wright MJ, Halton JM, Barr RD: Limitation of ankle range of motion in survivors of acute lymphoblastic leukemia: a cross-sectional study. Med Pediatr Oncol 32:279-82, 1999
139. Lehtinen SS, Huuskonen UE, Harila-Saari AH, et al: Motor nervous system impairment persists in long-term survivors of childhood acute lymphoblastic leukemia. Cancer 94:2466-73, 2002
140. Reinders-Messelink HA, Schoemaker MM, Hofte M, et al: Fine motor and handwriting problems after treatment for childhood acute lymphoblastic leukemia. Med Pediatr Oncol 27:551-5, 1996
141. McHale K, Cermak SA: Fine motor activities in elementary school: preliminary findings and provisional implications for children with fine motor problems. . Am J Occup Ther 46:898-903, 1992
142. Feder KP, Majnemer A: Handwriting development, competency, and intervention. Dev Med Child Neurol 49:312-7, 2007
143. Ness KK, Bhatia S, Baker KS, et al: Performance limitations and participation restrictions among childhood cancer survivors treated with hematopoietic stem cell transplantation: the bone marrow transplant survivor study. Arch Pediatr Adolesc Med 159:706-13, 2005

144. Ness KK, Leisenring WM, Huang S, et al: Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. . Cancer 115:1984-94, 2009
145. Beenakker EA, Maurits NM, Fock JM, et al: Functional ability and muscle force in healthy children and ambulant Duchenne muscular dystrophy patients. Eur J Paediatr Neurol 9:387-93, 2005
146. Hartman A, van den Bos C, Stijnen T, et al: Decrease in motor performance in children with cancer is independent of the cumulative dose of vincristine. Cancer 106:1395-401, 2006
147. Wright MJ, Hanna SE, Halton JM, et al: Maintenance of ankle range of motion in children treated for acute lymphoblastic leukemia. Pediatr Phys Ther 15:146-52, 2003
148. Tabrizi P, McIntyre WM, Quesnel MB, et al: Limited dorsiflexion predisposes to injuries of the ankle in children. J Bone Joint Surg Br 82:1103-6, 2000
149. Christiansen CL: The effects of hip and ankle stretching on gait function of older people. Arch Phys Med Rehabil 89:1421-8,, 2008
150. Moseley AM, Crosbie J, Adams R: High- and low-ankle flexibility and motor task performance. Gait Posture 18:73-80, 2003
151. Kibler WB, Goldberg C, Chandler TJ: Functional biomechanical deficits in running athletes with plantar fasciitis. Am J Sports Med 19:66-71, 1991
152. Wiesler ER, Hunter DM, Martin DF, et al: Ankle flexibility and injury patterns in dancers. Am J Sports Med 24:754-7, 1996
153. Payne KA, Berg K, Latin RW: Ankle Injuries and Ankle Strength, Flexibility, and Proprioception in College Basketball Players. J Athl Train 32:221-225, 1997
154. Stephens RJ, Hopwood P, Girling DJ, et al: Randomized trials with quality of life endpoints: are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? Qual Life Res 6:225-36, 1997
155. Sloan JA, Berk L, Roscoe J, et al: Integrating patient-reported outcomes into cancer symptom management clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. J Clin Oncol 25:5070-7, 2007
156. Blankenburg M, Boekens H, Hechler T, et al: Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. Pain 149:76-88, 2010
157. Molenaar HM, Zuidam JM, Selles RW, et al: Age-specific reliability of two grip-strength dynamometers when used by children. J Bone Joint Surg Am 90:1053-9, 2008
158. Beenakker EA, van der Hoeven JH, Fock JM, et al: Reference values of maximum isometric muscle force obtained in 270 children aged 4-16 years by hand-held dynamometry. Neuromuscul Disord 11(5):441-6, 2001
159. Evans AM, Scutter SD: Sagittal plane range of motion of the pediatric ankle joint: a reliability study. J Am Podiatr Med Assoc 96:418-22, 2006
160. The President's Council on Physical Fitness and Sports. Retrieved May 10, 2010, from http://www.fitness.gov/. 2010
161. Geiger R, Strasak A, Treml B, et al: Six-minute walk test in children and adolescents. J Pediatr 150:395-9, 399 e1-2, 2007