

Efficacy and Toxicity of Pegaspargase and Calaspargase Pegol in Childhood Acute Lymphoblastic Leukemia: Results of DFCI 11-001

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PURPOSE Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia (ALL) Consortium Protocol 11-001 assessed efficacy and toxicity of calaspargase pegol (calaspargase), a novel pegylated asparaginase formulation with longer half-life, compared with the standard formulation pegaspargase.

METHODS Patients age 1 to ≤ 21 years with newly diagnosed ALL or lymphoblastic lymphoma were randomly assigned to intravenous pegaspargase or calaspargase, 2,500 IU/m²/dose. Patients received one induction dose. Beginning week 7, pegaspargase was administered every 2 week for 15 doses and calaspargase every 3 week for 10 doses (30 weeks). Serum asparaginase activity (SAA) (≥ 0.1 IU/mL considered therapeutic) was assessed 4, 11, 18, and 25 days after the induction dose and before each postinduction dose.

RESULTS Between 2012 and 2015, 239 eligible patients enrolled (230 ALL, nine lymphoblastic lymphoma); 120 were assigned to pegaspargase and 119 to calaspargase. After the induction dose, SAA was ≥ 0.1 IU/mL in $\geq 95\%$ of patients on both arms 18 days after dosing. At day 25, more patients had SAA ≥ 0.1 IU/mL with calaspargase (88% v 17%; $P < .001$). Postinduction, median nadir SAAs were similar (≥ 1.0 IU/mL) for both arms. Of 230 evaluable patients, 99% of pegaspargase and 95% of calaspargase patients achieved complete remission ($P = .12$), with no difference in frequency of high end-induction minimal residual disease among evaluable patients with B acute lymphoblastic leukemia (B-ALL). There were no differences in frequencies of asparaginase allergy, pancreatitis, thrombosis, or hyperbilirubinemia. With 5.3 years median follow-up, 5-year event-free survival for pegaspargase was 84.9% (SE $\pm 3.4\%$) and 88.1% ($\pm$ SE 3.0%) for calaspargase ($P = .65$).

CONCLUSION Every 3-week calaspargase had similar nadir SAA, toxicity, and survival outcomes compared with every 2-week pegaspargase. The high nadir SAA observed for both preparations suggest dosing strategies can be further optimized.

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INTRODUCTION

L-asparaginase is an important component of therapy for childhood acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL); however, its use is associated with significant toxicities, including pancreatitis, thrombosis, and allergy.¹⁻⁵ Despite decades of experience, the optimal formulation and schedule of L-asparaginase to maximize efficacy and minimize toxicity remain unclear.

Intravenously (IV) administered polyethylene glycosylated-asparaginase (pegaspargase), a preparation formed by covalently attaching polyethylene glycol to the native *Escherichia coli* (*E. coli*) enzyme, is similarly effective as intramuscularly administered native *E. coli* asparaginase.⁶⁻⁹ Calaspargase pegol (calaspargase) is a novel pegylated L-asparaginase formulation that contains the same *E. coli* L-asparaginase enzyme and

polyethylene glycol moiety as pegaspargase but a different linker molecule. Calaspargase contains a succinimidyl carbamate linker that replaces the succinimidyl succinate linker of pegaspargase, resulting in a more hydrolytically stable formulation with longer half-life.^{10,11}

Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocol 11-001 (online only) assessed the feasibility and safety of administering calaspargase compared with standard pegaspargase in children and adolescents with newly diagnosed ALL or LL during induction and postinduction treatment phases. In postinduction, we assessed every 3-week administration of calaspargase on the basis of this agent's longer half-life, compared with pegaspargase administered every 2 weeks, according to our previously published treatment regimen.^{9,11} We report here results of the DFCI 11-001 trial.

ASSOCIATED

CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

DFCI 11-001 assessed the feasibility and safety of administering calaspargase, a novel pegylated L-asparaginase formulation, compared with pegaspargase in children and adolescents with newly diagnosed acute lymphoblastic leukemia or lymphoblastic lymphoma during induction and postinduction treatment phases.

Knowledge Generated

Calaspargase was associated with more sustained serum asparaginase activity (SAA) but was no more toxic than pegaspargase and appeared similarly effective. During postinduction treatment phases, every 3-week calaspargase had similar nadir SAA, toxicity, and survival outcomes compared with every 2-week pegaspargase, with median nadir SAA > 1.0 IU/mL for both preparations.

Relevance

Our results suggest that calaspargase may feasibly be used during induction therapy, without excess toxicity or significant impact on end-induction response. Given its longer half-life, calaspargase can be dosed less frequently than pegaspargase, especially in regimens that aim to achieve prolonged asparagine depletion. The high nadir SAA levels observed for both preparations suggest dosing strategies can be further optimized.

METHODS

Study Design and Patients

DFCI 11-001 was a phase III, multicenter, randomized clinical trial comparing the serum asparaginase activity (SAA) and toxicity of calaspargase and pegaspargase in the context of multiagent therapy for childhood ALL and LL. Patients age 1-21 years with newly diagnosed B acute lymphoblastic leukemia (B-ALL) or T-ALL (excluding mature B-cell phenotype) or LL were eligible. Institutional review boards at each participating institution (Appendix Table A1, online only) approved the Protocol before enrolling patients. Informed consent was obtained from parents or guardians, or patients (as age-appropriate) prior to enrollment and therapy initiation.

Risk Groups, Cytogenetics, and Minimal Residual Disease Assessment

At study entry, patients were assigned an initial risk group. Initial standard risk classification required age < 10 years, presenting WBC < 50,000 cells/ μ L, B-immunophenotype, and diagnostic CSF sample with < 5 WBC/high-powered field without (CNS-1) or with (CNS-2) lymphoblasts. Patients with age $\geq$ 10 years, presenting WBC $\geq$ 50,000 cells/ μ L, T-cell immunophenotype, or diagnostic CSF with lymphoblasts and $\geq$ 5 WBC/high-powered field (CNS-3) were classified as initial high risk (HR).

All cases were screened for cytogenetic abnormalities by karyotype, fluorescent in situ hybridization and/or polymerase chain reaction. Adverse cytogenetics were defined as presence of *KMT2A* rearrangement or hypodiploidy (< 44 chromosomes). Patients with Philadelphia chromosome-positive (Ph+) ALL were removed from trial by induction day 15 for alternative therapy. Among patients with ALL, end-induction minimal residual disease (MRD) from bone marrow aspirate samples was assessed by real-

time quantitative polymerase chain reaction as previously described.¹² Results were reported as the ratio of copy numbers of target gene to GAPDH and $\geq 10^{-3}$ (≥ 0.001) was considered high end-induction MRD.

Patients with high end-induction MRD (B-ALL only), adverse cytogenetics, and/or early T-cell precursor (ETP) phenotype were reclassified as very high risk (VHR). Final risk group was otherwise the same as initial risk grouping. Risk group for LL was based on the same parameters (without WBC or MRD).

Therapy

DFCI 11-001 treatment is summarized in Figure 1 and Appendix Table A2 (online only). All patients received a 4-week multiagent induction. Remission assessment was performed on day 32. For ALL, complete remission (CR) was defined as < 1% marrow malignant lymphoblasts with peripheral blood count recovery and absence of extramedullary disease. For LL, CR required $\geq$ 70% reduction in size of the largest nodes and/or masses, normalization of physical examination, and no CSF or marrow disease. Patients with persistent morphologic leukemia ($\geq$ 1% leukemic blasts in marrow) or < 70% reduction in size of the largest nodes and/or masses at end-induction were classified as induction failure (IF) and removed from the study. For all others, total planned duration of treatment was 24 months from CR date.

Asparaginase Random Assignment

At study entry, patients were randomly assigned, in a 1:1 ratio, to receive either pegaspargase or calaspargase, 2,500 IU/m²/dose, infused IV over 1-2 hours. Random assignment was stratified by age, initial risk group, and disease type (ALL or LL). Patients received a single dose of pegaspargase or calaspargase on day 7 of induction. Beginning week 7 of treatment, pegaspargase was administered every 2 weeks for 15 doses or calaspargase was

Prophase	Induction	Consolidation I	CNS phase	Consolidation II	Continuation
3 days	4 weeks Calaspargase or pegaspargase on day 7 on the basis of random assignment	3 weeks (9 weeks for VHR group, with addition of consolidation IB and IC)	3 weeks Calaspargase every 3 weeks or pegaspargase every 2 weeks, over 30 weeks on the basis of random assignment (postinduction asparaginase begins during consolidation IC for VHR group)	27 weeks	71 weeks (approximately 65 weeks for VHR group)

FIG 1. DFCI 11-001 treatment schema. DFCI, Dana-Farber Cancer Institute; VHR, very high risk.

administered every 3 weeks for 10 doses, for 30 consecutive weeks.

SAA Assessment

SAA was quantified using a validated assay as previously described¹³ and assessed 4, 11, 18, and 25 days after the induction asparaginase dose. Nadir serum asparaginase activity (NSAA) was assessed prior to each postinduction dose and compared between arms at weeks 7, 13, 19, and 25 after starting postinduction asparaginase (at weeks of nadir alignment). Serum asparaginase levels ≥ 0.1 IU/mL were considered therapeutic.¹⁴ Nondetectable NSAA (< 0.025 IU/mL) on two consecutive measurements was considered silent inactivation, prompting switch to *Erwinia* asparaginase.

Adverse Event and Toxicity Assessment

Toxicity was prospectively graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.¹⁵ Adverse events with targeted collection included asparaginase-related allergy (all grades), pancreatitis ($\geq$ grade 2), thrombosis or bleeding complications ($\geq$ grade 2), infection ($\geq$ grade 2), symptomatic osteonecrosis ($\geq$ grade 2), bone fracture (all grades), and seizure (all grades). Osteonecrosis, bone fracture, and thrombosis were confirmed with imaging. Pancreatitis was further defined as severe (symptoms with enzyme elevation for ≥ 72 hours and/or development of pancreatic pseudocyst or life-threatening complication), or mild or moderate (symptoms < 72 hours with enzyme elevation). All other grade 4 or 5 adverse events were collected, excluding grade 4 hematologic toxicity.

Statistical Methods

The primary feasibility end point was the proportion of patients in postinduction therapy with NSAA ≥ 0.1 IU/mL. The study had 89% power to detect a 10% reduction in the proportion of patients with at least one NSAA ≥ 0.1 IU/mL during the postinduction asparaginase consolidation phases between arms using a one-sided 0.025 significance level and 96% power to detect a mean difference of 0.15 IU/mL in asparaginase enzyme activity level at the week 7 time point using a two-sided *t* test assuming a standard deviation of 0.3.

The primary toxicity end point was the overall frequency of asparaginase-related toxicity, defined as asparaginase allergy, pancreatitis, and thrombotic or bleeding event. The study was designed to monitor the overall frequency of asparaginase-related toxicity of each arm compared with the historical control arm of IV pegaspargase on the prior Protocol, DFCI 05-001 (overall toxicity rate 27%). The design required 240 randomly assigned patients to allow an estimated 112 evaluable patients on each arm; 34% (exact two-sided 80% CI, 28 to 40) patients on either arm experiencing asparaginase-related toxicity would differ from historic control.

Fisher's exact test and Wilcoxon rank-sum test were used to compare patient characteristics by groups for categorical and continuous variables, respectively. Event-free survival (EFS) was defined as time from random assignment to relapse, subsequent malignant neoplasm, or death (whichever occurred first). IF and death were considered events at time zero. Toxicity and time-to-event analyses were performed by intention-to-treat. Overall survival (OS) was calculated from time of random assignment to death from any cause. EFS and OS were estimated using the method of Kaplan and Meier and compared between groups with the log-rank test. Incidence of osteonecrosis and bone fracture was estimated by the cumulative incidence method, identifying remission deaths and relapse as competing risks. Cumulative incidence was estimated with the cuminc utility in the 'cmprsk' package in R and tested using Gray's test. *P* values were two-sided and considered significant with a value $< .05$.

RESULTS

Patients, Induction Events, and Risk Group Stratification

Between June 3, 2012, and June 8, 2015, 240 patients enrolled (Fig 2). Of these, 121 patients were randomly assigned to pegaspargase and 119 to calaspargase. One patient from the pegaspargase arm was found ineligible (for ambiguous leukemia lineage) and removed from the study. There were no significant differences in presenting patient characteristics among eligible patients by random assignment (Table 1), although there were more cases of

ETV6-RUNX1 on the calaspargase arm. One patient from each arm withdrew consent prior to remission assessment. Four pegaspargase-assigned patients and three from the calaspargase arm were diagnosed with Ph+ ALL and removed.

Of the 230 patients evaluable for induction events, 109 of 115 patients (95%) on the calaspargase arm and 114 of 115 patients (99%) on the pegaspargase arm achieved CR ($P = .12$). There was one IF on the pegaspargase arm and four IF and two deaths on the calaspargase arm. Among patients with B-ALL and evaluable MRD, there was no difference in frequency of high end-induction MRD by treatment arm (10% calaspargase and 11% pegaspargase; $P = .99$).

Final risk group classification included 63 final standard risk patients on each arm, 37 final HR patients on the calaspargase arm, and 39 on the pegaspargase arm. Twenty-one patients changed to the final VHR group (nine calaspargase and 12 pegaspargase). Within the calaspargase arm, three patients changed to VHR because of *KMT2A* rearrangement (one also with high end-induction MRD) and six additional patients because of high MRD. On the pegaspargase arm, one patient changed to VHR because of hypodiploidy, nine for high MRD, and two for ETP T-ALL.

SAA

Median SAA after administration of a single dose of calaspargase or pegaspargase on day 7 of induction, measured exactly 4, 11, 18, and 25 days after the dose, is displayed in Figure 3A. SAA remained ≥ 0.1 IU/mL in $\geq 95\%$ of patients on both arms through induction day 25, 18 days after the dose. However, 25 days after dosing, a higher proportion of calaspargase patients had therapeutic SAA (≥ 0.1 IU/mL) compared with pegaspargase (88% v 17%; $P < .001$). Median SAA was higher (0.319 IU/mL v 0.056 IU/mL; $P < .001$) with calaspargase compared with pegaspargase measured 25 days after the induction dose (Table 2). Results were similar when including samples obtained within 3 days of the exact designated time point (Appendix Table A3, online only).

Median NSAA at 7, 13, 19, and 25 weeks after starting postinduction asparaginase was similar between the two preparations and ≥ 1.0 IU/mL at these time points on both arms (Table 2 and Fig 3B). Two patients on the calaspargase arm met Protocol criteria for silent inactivation. All other evaluable patients had NSAA ≥ 0.1 IU/mL throughout the 30-week consolidation (Table 2), and the majority had NSAA ≥ 1.0 IU/mL (Appendix Table A4, online only).

Toxicity and Adverse Events

The frequency of postinduction asparaginase toxicity (allergy, pancreatitis, and thrombosis or bleeding) was 37.6% (two-sided 80% CI, 31.5 to 44.2) and 37.7% (two-sided 80% CI, 31.7 to 44.1) for calaspargase and pegaspargase, respectively. There were no differences between arms in

the frequencies of individual toxicities of asparaginase allergy, pancreatitis, thrombosis, or hyperbilirubinemia during induction or postinduction treatment phases (Table 3). Postinduction asparaginase toxicity frequency on each of the DFCI 11-001 arms was higher than the final frequency of 28% on the historical control DFCI 05-001 pegaspargase arm (Appendix Table A5, online only). When exploring each individual toxicity of asparaginase allergy, pancreatitis, or thrombosis, there were no significant differences by each DFCI 11-001 treatment arm compared with the historical control, although frequency of thrombosis was numerically higher on DFCI 11-001.

On the calaspargase arm, 68 of 109 patients who achieved CR (62%) received the full planned 30-week treatment course with calaspargase; an additional 19 patients (18%) completed a full asparaginase course having switched to *Erwinia* for clinical allergy or silent inactivation. Reasons patients did not complete 30 weeks of asparaginase on the calaspargase arm were as follows: 13 pancreatitis, two thrombosis, one hyperbilirubinemia, one remission death, three withdrawals, one received a single pegaspargase dose in error, and one unknown. In total, 91 patients (83%) on the calaspargase arm completed ≥ 26 weeks of asparaginase (including *Erwinia*). On the pegaspargase arm, 83 of 114 patients who achieved CR (73%) received the complete 30 week of pegaspargase; an additional 16 (14%) completed a full asparaginase course having switched to *Erwinia* for clinical allergy. Reasons patients did not complete 30 weeks on the pegaspargase arm were as follows: 13 pancreatitis, one thrombosis, and one withdrawal. In total, 99 (87%) on the pegaspargase arm completed ≥ 26 weeks of asparaginase (including *Erwinia*). In exploratory analyses, there were no significant differences between arms in the completion of 30 weeks of assigned asparaginase ($P = .12$), 30 weeks including *Erwinia* ($P = .21$), or ≥ 26 weeks including *Erwinia* ($P = .57$).

Events and Survival Outcomes

Among those who achieved CR, there were five relapses (5%) on the calaspargase arm and 16 (14%) on the pegaspargase arm. There were three deaths in remission on the calaspargase arm (Appendix Table A6, online only).

For the overall cohort, with 5-year median follow-up, 5-year EFS was 86.5 (SE $\pm$ 2.3) and 5-year OS was 94.9 (SE $\pm$ 5.1). Appendix Table A7 (online only) shows EFS on the basis of presenting characteristics. The 5-year EFS for calaspargase was 88.1% (SE $\pm$ 3.0) and 84.9% (SE $\pm$ 3.4) for pegaspargase ($P = .65$). Five-year OS was 94.0% (SE $\pm$ 2.2) for calaspargase and 95.8% (SE $\pm$ 1.9) for pegaspargase ($P = .72$) (Fig 4).

DISCUSSION

DFCI 11-001 assessed the safety and feasibility of administering calaspargase compared with pegaspargase in

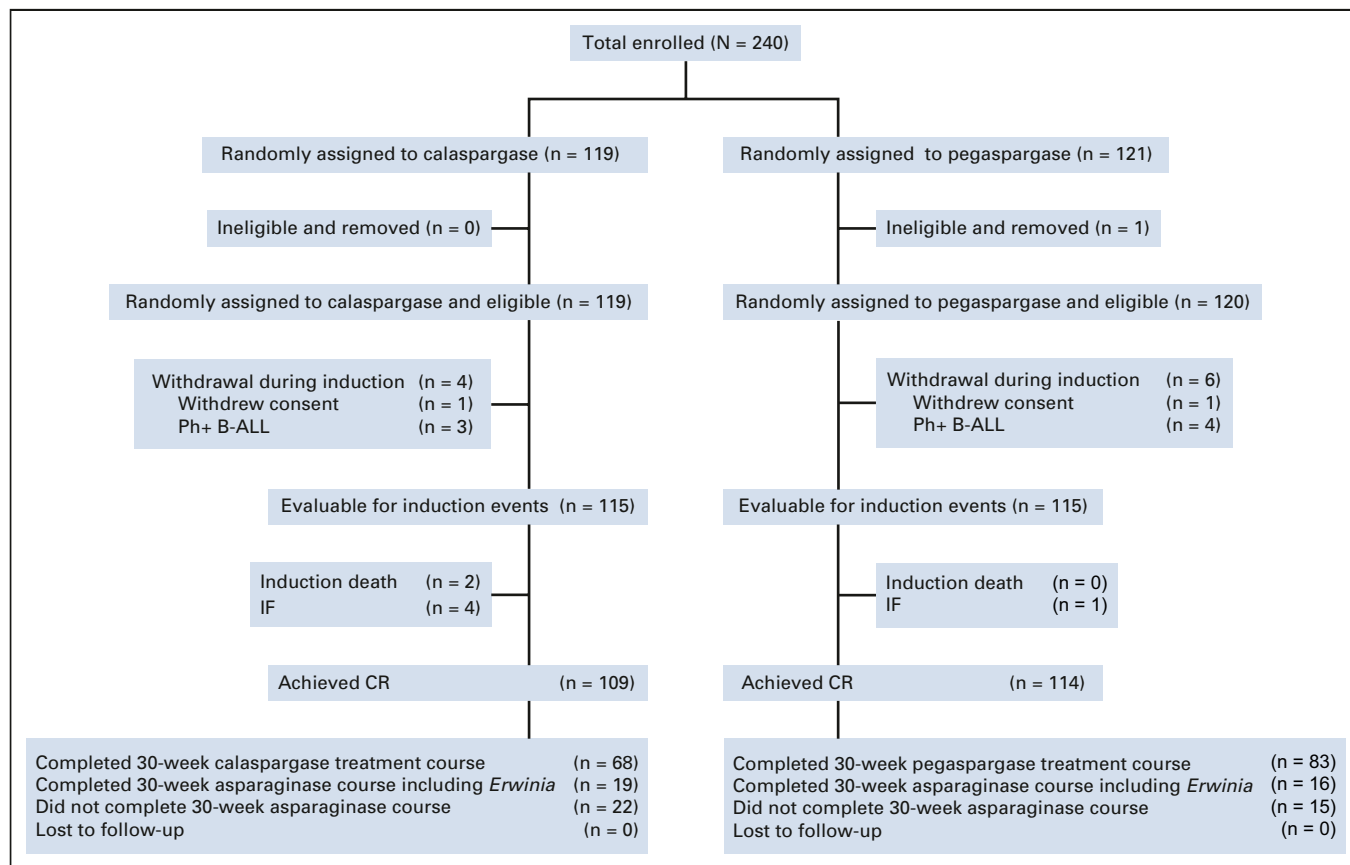


FIG 2. DFCI 11-001 CONSORT diagram. No patients were excluded from analysis except the one ineligible patient. B-ALL, B acute lymphoblastic leukemia; CR, complete remission; DFCI, Dana-Farber Cancer Institute; IF, induction failure; Ph+, Philadelphia chromosome-positive.

children and adolescents with newly diagnosed ALL and LL during induction and postinduction treatment phases. We report that every 3-week calaspargase had similar nadir SAA, toxicity, and survival outcomes compared with every 2-week pegaspargase. These results informed the US Food and Drug Administration approval of calaspargase for pediatric patients with ALL.

In this study, we confirmed that calaspargase has more sustained activity than pegaspargase. More than 3 weeks after a single dose of calaspargase given during induction, SAA was higher than after a dose of pegaspargase, and more patients had SAA at or above the 0.1 IU/mL therapeutic threshold. These findings are consistent with results from the Children's Oncology Group (COG) protocol AALL07P4. On the COG study, 95% of patients receiving an induction dose of calaspargase (2,500 IU/m²) had activity levels $\geq$ 0.1 IU/mL 25 days after the dose compared with 28.6% of those receiving pegaspargase, similar to our findings.¹¹ We did not demonstrate that the more prolonged asparaginase activity associated with calaspargase affected induction response; there were no differences between arms in CR rate or the proportion of patients with high end-induction MRD. In addition, despite higher and more prolonged SAA, calaspargase did not appear associated with increased induction toxicity.

We also demonstrated that calaspargase may be given less frequently than pegaspargase during postinduction therapy, with similar NSAA and efficacy (as assessed by EFS). With both preparations, median NSAA was consistently $\geq$ 1.0 IU/mL on both arms, 10 times higher than the goal therapeutic NSAA of 0.1 IU/mL. The high NSAA levels observed for both preparations suggest dosing strategies can be further optimized. Kloos et al¹⁶ recently demonstrated that reduced dosing of pegaspargase was still associated with therapeutic asparaginase levels, within the Dutch Childhood Oncology Group ALL-11 protocol. In our current trial, DFCI 16-001, we are assessing individualized dosing of pegaspargase on the basis of NSAA.

Asparaginase-related hypersensitivity was observed in 15% of patients on this trial, with no difference between preparations. The majority of hypersensitivity reactions occurred with the second or third dose of pegaspargase; only four (1.7%) patients experienced clinical hypersensitivity with subsequent doses. Premedication to prevent clinical hypersensitivity was not used on DFCI 11-001. All patients with clinical hypersensitivity were switched to *Erwinia*; however, this strategy is problematic because of the short half-life of *Erwinia*, with need for more frequent dosing, and recurrent issues with drug shortage. On trial DFCI 16-001,

TABLE 1. Baseline Characteristics on the Basis of Randomly Assigned Asparaginase Arm of DFCI 11-001

Characteristic	Overall, n (%)	Calaspargase, n (%)	Pegaspargase, n (%)	P
Total, n	239	119	120	
Age at diagnosis, years				
< 10	179 (75)	89 (75)	90 (75)	.99
≥ 10	60 (25)	30 (25)	30 (25)	
Median (range)	5.2 (1.0-20.9)	5.6 (1.0-20.9)	5.1 (1.0-18.8)	
Sex				
Male	147 (62)	76 (64)	71 (59)	.51
Female	92 (38)	43 (36)	49 (41)	
Diagnosis				
ALL	230 (96)	114 (96)	116 (97)	.75
LL	9 (4)	5 (4)	4 (3)	
Immunophenotype				
B-immunophenotype	207 (87)	103 (87)	104 (87)	.99
T-immunophenotype ^a	32 (13)	16 (13)	16 (13)	
Initial DFCI risk group				
SR	141 (59)	70 (59)	71 (59)	.99
HR	98 (41)	49 (41)	49 (41)	
WBC ^b at diagnosis, cells/ μ L				
< 50,000	189 (82)	93 (82)	96 (83)	.86
≥ 50,000	41 (18)	21 (18)	20 (17)	
CNS status at diagnosis				
CNS 1	189 (79)	90 (76)	99 (83)	.24
CNS 2	34 (14)	19 (16)	15 (13)	
CNS 3	4 (2)	1 (1)	3 (3)	
Traumatic with blasts	5 (2)	3 (3)	2 (2)	
Traumatic without blasts	7 (3)	6 (5)	1 (1)	
Anterior mediastinal mass	19 (8)	7 (6)	12 (10)	.34
Down syndrome	8 (3)	3 (3)	5 (4)	.72
Cytogenetics, n evaluable	235 (98)	116	119	
<i>BCR-ABL1</i>	7 (3)	3 (3)	4 (3)	.99
Hyperdiploidy (51-65 chromosomes)	63 (26)	30 (26)	33 (28)	.77
Trisomies, chromosomes 4 and 10	39 (17)	20 (17)	19 (16)	.86
<i>ETV6-RUNX1</i>	50 (21)	32 (27)	18 (15)	.025
Hypodiploidy (< 44 chromosomes)	1 (0.4)	0 (0)	1 (1)	.99
<i>KMT2A</i> -rearranged	3 (1)	3 (3)	0 (0)	.12
iAMP21	11 (5)	2 (2)	9 (8)	.060
<i>TCF3-PBX1</i>	3 (1)	1 (1)	2 (2)	.99
Normal karyotype	24 (10)	16 (13)	8 (7)	.087
Final DFCI risk group ^c				
SR	126	63	63	.85
HR	76	37	39	
VHR	21	9	12	

Abbreviations: ALL, acute lymphoblastic leukemia; CR, complete remission; DFCI, Dana-Farber Cancer Institute; HR, high risk; LL, lymphoblastic leukemia; SR, standard risk; VHR, very high risk.

^aAmong T-immunophenotype cases, there were two cases per arm with early T-cell precursor phenotype.

^bWBC presented for patients with ALL.

^cFinal DFCI risk group includes 223 non-Philadelphia chromosome-positive patients who achieved CR (total 109 calaspargase arm; 114 pegaspargase arm).

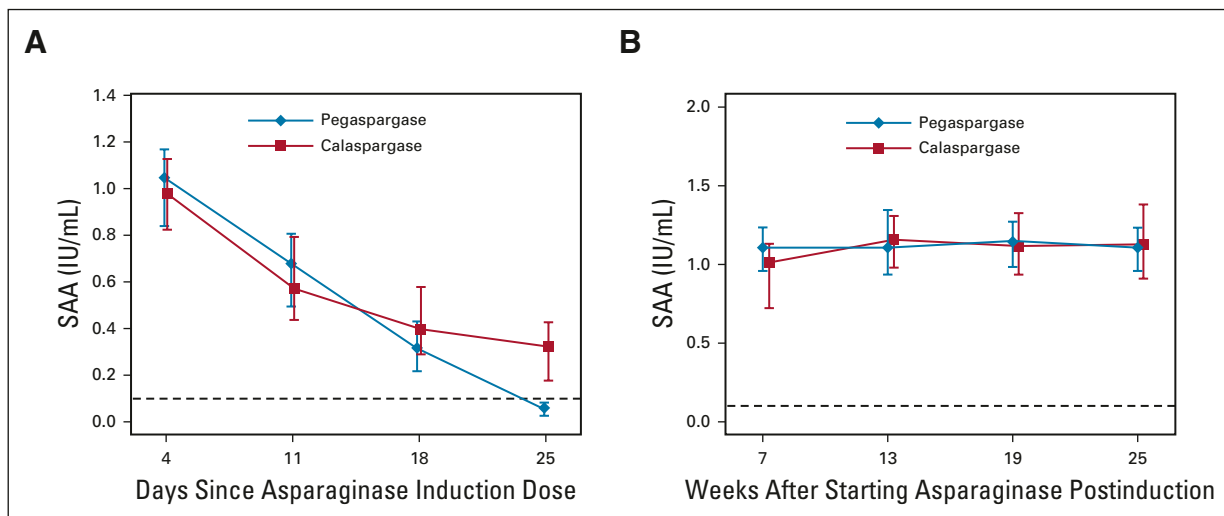


FIG 3. SAA. (A) Median SAA after administration of a single dose of calaspargase or pegaspargase (according to random assignment) on day 7 of induction, measured 4, 11, 18, and 25 days after the dose (corresponding to days 11, 18, 25, and 32). (B) Postinduction median nadir asparaginase activity at weeks 7, 13, 19, and 25 after starting postinduction asparaginase. Error bars represent 25th and 75th percentiles, and dashed line indicates serum asparaginase level of 0.1 IU/mL (considered therapeutic threshold). SAA, serum asparaginase activity.

we are rechallenging patients with CTCAE grade 2 hypersensitivity to pegaspargase.¹⁷ If, with premedication, patients do not experience a subsequent allergic reaction and have therapeutic SAA, they continue pegaspargase; otherwise, they are switched to *Erwinia*. Universal premedication prior to pegaspargase with rigorous therapeutic drug monitoring is another strategy with the potential to reduce the frequency of switching to *Erwinia*.¹⁸ We previously reported that approximately 10% of patients treated with native *E. coli* L-asparaginase experienced silent inactivation and that switching such patients to *Erwinia* may lead to improved outcome.¹⁹ On the 11-001 trial, only two of 239 patients (0.8%) met Protocol definition of silent

inactivation, suggesting the frequency of this problem is lower with use of pegylated asparaginase.

Although we observed no difference in asparaginase-associated toxicity between arms on DFCI 11-001, the overall rate of these toxicities was higher on this trial compared with the predecessor, DFCI 05-001, whose treatment backbone was nearly identical to the DFCI 11-001 pegaspargase arm. The relationship to historic control toxicity rate did not differ by treatment arm, with overall higher rates of combined asparaginase-associated toxicity on each DFCI 11-001 arm compared with 05-001. The higher overall toxicity rate may be because of different grading systems (CTCAE 3.0 for DFCI 05-001 v CTCAE 4.0

TABLE 2. SAA Levels During Induction Phase and Postinduction Phases

Timing	n		Median SAA, IU/mL (range)		% of Patients With SAA $\geq$ 0.1 IU/mL	
	Calaspargase	Pegaspargase	Calaspargase	Pegaspargase	Calaspargase	Pegaspargase
Induction, ^a days						
4	77	79	0.975 (0.430-1.499)	1.045 (0.069-1.731)	100	99
11	60	60	0.571 (0.156-1.176)	0.673 (0.025-1.224)	100	98
18	62	60	0.394 (0.080-0.887)	0.314 (0.025-0.536)	98	95
25	42	47	0.319 (0.025-0.549)	0.056 (0.025-0.079)	88	17
Postinduction ^b						
Week 7	79	92	1.006 (0.025-1.948)	1.097 (0.506-1.814)	97	100
Week 13	74	82	1.147 (0.143-2.181)	1.101 (0.512-1.866)	100	100
Week 19	72	79	1.110 (0.318-2.709)	1.134 (0.508-1.820)	100	100
Week 25	73	83	1.117 (0.153-2.106)	1.109 (0.483-1.814)	100	100

Abbreviation: SAA, serum asparaginase activity.

^aDays after asparaginase administration on day 7 of induction.

^bNadir serum asparaginase level designated weeks after first postinduction dose of asparaginase.

TABLE 3. Adverse Events During Induction Phase and Postinduction Phases Among Randomly Assigned Patients

Adverse Event	Induction			Postinduction ^a		
	Calaspargase	Pegaspargase	P	Calaspargase	Pegaspargase	P
	n (%)	n (%)		n (%)	n (%)	
Total n	119	120		109	114	
Asparaginase toxicity	7 (6)	15 (13)	.12	41 (37.6)	43 (37.7)	1.00
Allergy (grade ≥ 2)	0	1 (1)	1.00	19 (17)	16 (14)	.58
Pancreatitis (grade ≥ 2)	3 (3)	4 (3)	1.00	14 (13)	17 (15)	.70
Mild or moderate	0	2 (2)	—	4 (4)	6 (5)	.75
Severe	3 (3)	2 (2)	—	11 (10)	12 (11)	1.00
Thrombosis (grade ≥ 2)	4 (3)	10 (8)	.17	15 (14)	14 (12)	.84
CNS	0	0	—	1 (1)	1 (1)	—
Non-CNS	4 (3)	10 (8)	.17	14 (13)	13 (11)	.84
Bleeding	0	0	—	1 (1)	0	—
Bacterial and/or fungal infection (grade ≥ 3)	17 (14)	16 (13)	.85	15 (14)	17 (15)	.85
Bacterial infection	14 (12)	11 (9)	.53	13 (12)	17 (15)	.56
Fungal infection	5 (4)	6 (5)	1.00	2 (2)	1 (1)	.61
Seizure (grade ≥ 2)	4 (3)	1 (1)	.21	3 (3)	1 (1)	.36
Hyperbilirubinemia (grade ≥ 4)	4 (3)	1 (1)	.21	4 (3)	3 (3)	.71
Bone fracture ^a (grade ≥ 2)	3 (3)	0	—	22.1 (± 3.8) ^a	23.7 (± 3.9) ^a	.93
Osteonecrosis ^b (grade ≥ 2)	0	0	—	8.7 (± 2.7) ^b	10.9 (± 2.9) ^b	.50

^aPostinduction results display 5-year cumulative incidence of bone fracture (90% CI).

^bPostinduction results display 5-year cumulative incidence of osteonecrosis (90% CI).

on 11-001) or potentially because of differences in data collection and monitoring of DFCI 11-001.

We previously reported that within a 30-week postinduction asparaginase treatment plan, completion of < 26 weeks of asparaginase was associated with inferior EFS.²⁰ Gupta et al,²¹ reporting on COG trials AALL0331 and AALL0232, also demonstrated that discontinuation of planned asparaginase was associated with inferior disease-free survival

for higher-risk patients but that patients able to complete planned asparaginase with substitution of *Erwinia* maintained favorable outcomes, highlighting the importance of asparaginase delivery. On DFCI 11-001, there was no significant difference between arms in completion of planned asparaginase; more than 80% of patients on each arm completed ≥ 26 weeks of asparaginase (including *Erwinia*).

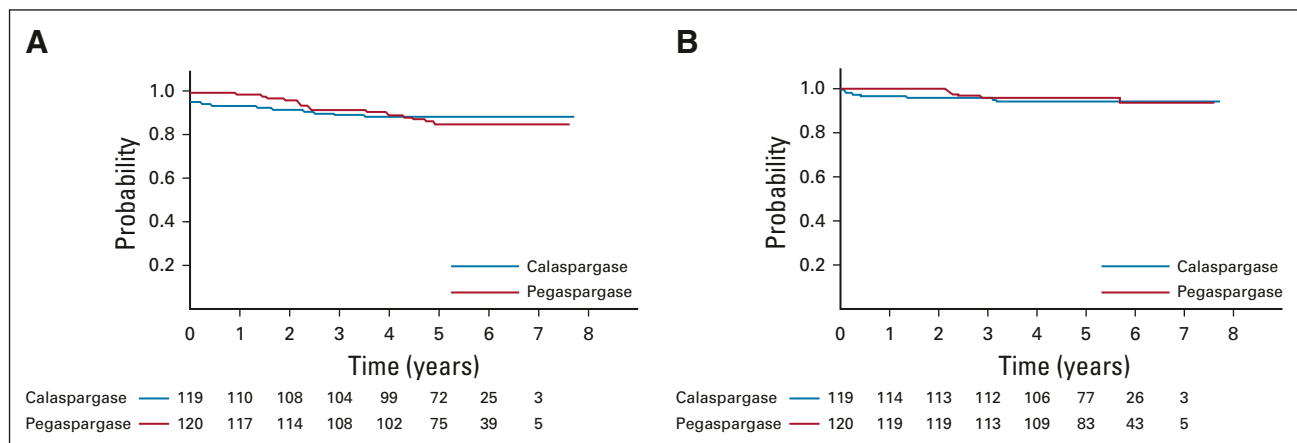


FIG 4. DFCI 11-001 survival outcomes. (A) EFS for all eligible patients on the basis of randomly assigned asparaginase arm. (B) OS for all eligible patients on the basis of randomly assigned asparaginase arm. DFCI, Dana-Farber Cancer Institute; EFS, event-free survival; OS, overall survival.

Our findings offer context for the use of calaspargase in other treatment regimens. Data from our induction phase, which is similar to many other regimens, provide strong evidence that calaspargase may feasibly be used during this phase without excess toxicity or significant impact on end-induction response. Our data also provide evidence of its safety during postinduction treatment phases, even in asparaginase-intensive regimens. Although definitive conclusions regarding EFS on DFCI 11-001 are limited by sample size, EFS between arms is similar, without suggestion that calaspargase is less efficacious than pegaspargase. However, whether calaspargase, with its longer half-life, might have more of an effect on toxicity or

leukemia outcomes within other regimens that use a more intermittent postinduction schedule of asparaginase requires further investigation.

In summary, we demonstrated that calaspargase is associated with more sustained SAA but was no more toxic than pegaspargase and appeared similarly effective. Given its longer half-life, calaspargase can be dosed less frequently than pegaspargase, especially in regimens that aim to achieve prolonged asparagine depletion. With the high NSAA observed, future trials should further address the efficacy and toxicity of lower doses of pegylated asparaginase preparations.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Toxicity of Pegaspargase and Calaspargase Pegol in Childhood Acute Lymphoblastic Leukemia: Results of DFCI 11-001

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APPENDIX

TABLE A1. Centers Participating in DFCI Protocol 11-001

Participating Institution	Location
Albert Einstein/Children's Hospital at Montefiore	Bronx, NY
Centre Hospitalier Universite de Quebec	Quebec City, QC, Canada
Columbia University Medical Center	New York, NY
DFCI/Boston Children's Hospital	Boston, MA
Hasbro Children's Hospital	Providence, RI
Hospital Sainte-Justine	Montreal, QC, Canada
Inova/Fairfax Hospital for Children	Falls Church, VA
McMaster University	Hamilton, ON, Canada
San Jorge Children's Hospital	San Jorge, Puerto Rico

Abbreviation: DFCI, Dana-Farber Cancer Institute.

TABLE A2. DFCI-ALL Protocol 11-001 Treatment Plan

Phase	Treatment Details
Remission induction 32 days	Steroid prophase (days 1-3) Methylprednisolone 32 mg/m²/day, given every 8 hours Remission induction therapy (days 4-32) VCR 1.5 mg/m² IV once per week (maximum 2 mg), days 4, 11, 18, and 25 Prednisone 40 mg/m²/day PO (or methylprednisolone 32 mg/m²/day IV), given every 8 hours, days 4-32 (followed by taper over < 7 days) DOX 30 mg/m²/dose IV, days 4 and 5 HR patients: with dexrazoxane 300 mg/m²/dose IV, days 4 and 5 MTX 40 mg/m² IV push on day 6 ASP according to random assignment on day 7 Calaspargase or pegaspargase, 2,500 IU/m² IV IT cytarabine dosed by age on day 1^a IT-MAH dosed by age on day 18 IT-M dosed by age on day 32
Consolidation I SR and HR: 3 weeks VHR: approximately 9 weeks	All patients: Consolidation IA VCR 2 mg/m² (maximum 2 mg), day 1 6-MP 50 mg/m²/day PO at bedtime, days 1-14 IT-M dosed by age, day 1^b High-dose MTX 5 mg/m² IV over 24 hours on day 1, followed by leucovorin rescue HR and VHR patients: same as SR patients with the addition of the following: DOX 30 mg/m²/dose IV on day 1 with dexrazoxane 300 mg/m²/dose IV VHR patients in addition to above also receive the following: Consolidation IB Cyclophosphamide 1,000 mg/m² IV over 1 hour, day 1 Cytarabine 75 mg/m²/day IV push, days 2-5 and 9-12 6-MP 50 mg/m²/day PO at bedtime, days 1-14 IT-M dosed by age, day 1 Consolidation IC Cytarabine 2 g/m²/dose IV every 12 hours for a total of four doses starting on day 1 Etoposide 100 mg/m²/dose IV daily, days 3, 4, and 5 DEX 18 mg/m²/day PO or IV divided twice daily, days 1-5 (10 doses total) ASP according to random assignment, beginning on day 8^c
CNS 3 weeks	All patients: VCR 2 mg/m² (maximum 2 mg) IV, day 1 6-MP 50 mg/m²/day PO at bedtime, days 1-14 DEX 6 mg/m²/day PO divided twice daily, days 1-5 IT-MAH dosed by age administered twice weekly starting on day 1 (four doses total) SR and HR patients: ASP according to random assignment starting on day 1^c HR and VHR patients in addition to above also receive the following: DOX 30 mg/m²/dose IV on day 1 administered with dexrazoxane 300 mg/m²/dose IV DEX increased to 18 mg/m²/day PO divided twice daily, days 1-5 Cranial radiation—only included for those CNS-3 at diagnosis, T-ALL, and VHR patients
Consolidation II Approximately 27 weeks	All patients: ASP according to random assignment, to complete 30 weeks of postinduction ASP Calaspargase, 2,500 IU/m² IV every 3 weeks to complete 10 postinduction doses or Pegaspargase 2,500 IU/m² IV every 2 weeks to complete 15 postinduction doses SR patients: every 3-week cycles VCR 2 mg/m² (maximum 2 mg) IV, day 1 6-MP 50 mg/m²/day PO at bedtime, days 1-14 DEX 6 mg/m²/day PO divided twice daily, days 1-5 MTX 30 mg/m² IV push or IM weekly, days 1, 8, and 15 (week 1 MTX omitted if IT MTX given) IT-MAH dosed by age given on day 1 every 9 weeks for six doses and then every 18 weeks HR and VHR patients: in addition to above (omitting weekly MTX until DOX is completed) receive the following: DOX 30 mg/m²/dose IV on day 1 administered with dexrazoxane 300 mg/m²/dose IV Once cumulative DOX reaches 300 mg/m², weekly MTX is substituted, as in the SR arm DEX dose increased to 18 mg/m²/day PO divided twice daily, days 1-5 10 cycles total, then decreased to 6 mg/m²/day, as in the SR arm Consolidation II ends when patient has achieved 30 weeks of asparaginase therapy and has reached cumulative DOX dose of 300 mg/m²

(continued on following page)

TABLE A2. DFCI-ALL Protocol 11-001 Treatment Plan (continued)

Phase	Treatment Details
Continuation Approximately 71 weeks	All patients receive every 3-week cycles of the following: VCR 2 mg/m² (maximum 2 mg) IV on day 1 6-MP 50 mg/m²/day PO at bedtime on days 1-14 DEX 6 mg/m²/day PO divided twice daily, days 1-5 MTX 30 mg/m² IV push or IM weekly, days 1, 8, and 15 (week 1 MTX held if IT MTX is given) IT-MAH dosed by age given on day 1 every 9 weeks for six doses and then every 18 weeks^d Continuation therapy concludes after 104 weeks of continuous CR

Abbreviations: 6-MP, 6-mercaptopurine; ALL, acute lymphoblastic leukemia; ASP, asparaginase; calaspargase, calaspargase pegol; CR, complete remission; DEX, dexamethasone; DFCI, Dana-Farber Cancer Institute; DOX, doxorubicin; HD-MTX, high-dose methotrexate; HR, high risk; IM, intramuscular; IT, intrathecal; IT-M, IT-methotrexate; IT-MAH, IT methotrexate/cytarabine/hydrocortisone; IV, intravenously; MTX, methotrexate; PO, orally; SR, standard risk; VCR, vincristine; VHR, very high risk.

^aPatients with CNS leukemia at diagnosis (CNS-2 and CNS-3) received IT cytarabine two times per week until CSF was clear of malignant cells on three consecutive examinations.

^bNot administered if high-dose-MTX started within 72 hours of ITM given on day 32 of induction.

^cAccording to random assignment: calaspargase 2,500 IU/m²/dose IV every 3 weeks (10 total doses) or pegaspargase 2,500 IU/m²/dose IV every 2 weeks (15 total doses). Continues at designated interval across treatment phases through consolidation II once started (within CNS phase for SR and HR patients, within consolidation IC for VHR patients).

^dIT-MAH administered every 18 weeks in Consolidation II and Continuation phases for those who received previous cranial radiation.

TABLE A3. SAA Levels During Induction Including Samples Obtained Within 3 Days

Timing	n		Median SAA, IU/mL (range)		% of Patients With SAA $\geq$ 0.1 IU/mL	
	Calaspargase	Pegaspargase	Calaspargase	Pegaspargase	Calaspargase	Pegaspargase
Induction, ^a days						
4	116	114	0.980 (0.430-1.499)	1.054 (0.069-1.731)	100	99
11	112	110	0.603 (0.144-1.176)	0.685 (0.025-1.224)	100	99
18	111	108	0.421 (0.025-0.887)	0.335 (0.025-0.752)	97	93
25	108	111	0.298 (0.025-1.025)	0.056 (0.025-0.223)	89	19

Abbreviation: SAA, serum asparaginase activity.

^aDays after asparaginase administration on day 7 of induction, including samples obtained within 3 days of designated assessment time point.

TABLE A4. SAA Levels During Induction and Postinduction: Percentage of Patients Achieving Designated Thresholds

Timing	n		% of Patients With SAA $\geq$ 0.025 IU/mL		% of Patients With SAA $\geq$ 0.1 IU/mL		% of Patients With SAA $\geq$ 0.4 IU/mL		% of Patients With SAA $\geq$ 1.0 IU/mL	
	SC-PEG	SS-PEG	SC-PEG	SS-PEG	SC-PEG	SS-PEG	SC-PEG	SS-PEG	SC-PEG	SS-PEG
Induction, ^a days										
4	77	79	100	100	100	99	100	99	44	57
11	60	60	100	98	100	98	80	90	5	7
18	62	60	100	97	98	95	48	30	0	0
25	42	47	98	88	88	17	33	0	0	0
Postinduction ^b										
Week 7	79	92	97	100	97	100	95	100	51	71
Week 13	74	83	100	100	100	100	97	100	73	65
Week 19	72	79	100	100	100	100	97	100	67	75
Week 25	73	83	100	100	100	100	97	100	67	70

Abbreviations: SAA, serum asparaginase activity; SC-PEG, calaspargase pegol; SS-PEG, pegaspargase.

^aDays after asparaginase administration on day 7 of induction.

^bWeeks after first postinduction dose of asparaginase.

TABLE A5. Postinduction Toxicity on DFCI 05-001 Intravenous Pegaspargase Arm and DFCI 11-001 Calaspargase and Pegaspargase Arms

Adverse Event	05-001 Pegaspargase (n = 232)		11-001 Pegaspargase (n = 114)			11-001 Calaspargase (n = 109)		
	n	%	n	%	<i>P</i> ^a	n	%	<i>P</i> ^a
Asparaginase toxicity	65	28	43	38	.084	41	38	.080
Asparaginase allergy (grade ≥ 2)	28	12	16	14	.86	19	17	.18
Pancreatitis (grade ≥ 2)	27	12	17	15	.40	14	13	.73
Thrombosis or bleeding (grade ≥ 2)	17	7	14	12	.11	15	14	.072
Bacterial and/or fungal infection (grade ≥ 3)	47	20	17	15	.24	15	14	.18
Seizure (grade ≥ 2)	3	1	1	1	.99	3	3	.39
Hyperbilirubinemia (grade ≥ 4)	2	1	3	3	.37	4	4	.085

Abbreviation: DFCI, Dana-Farber Cancer Institute.

^aComparison with historical control DFCI 05-001 pegaspargase arm. Two-sided 80% CI used for trial monitoring.

TABLE A6. DFCI 11-001 Outcome Events Among Randomly Assigned Patients

Events	Calaspargase, n (%)	Pegaspargase, n (%)
Total eligible patients	119	120
Withdrawal during induction	4 (3)	5 (4)
Withdrew consent	1 (1)	1 (1)
Ph+ (removed day 15)	3 (2)	4 (3)
Total evaluable for induction events	115	115
Induction death ^a	2 (2) ^b	0 (0)
IF ^a	4 (3) ^b	1 (1) ^b
Achieved CR ^a	109 (95)	114 (99)
Relapse ^c	5 (5)	16 (14)
Remission death ^c	3 (3)	0
Subsequent malignancy	0	0
Achieved CR, LL	5	4
Achieved CR, B-ALL	95	98
No. of evaluable for MRD, B-ALL ^d	80	83
End-induction MRD (≥ 0.001)	8 (10)	9 (11)
End-induction MRD (≥ 0.0001)	27 (34)	23 (28)
Achieved CR, T-ALL	9	12
No. of evaluable for MRD, T-ALL ^e	7	9
End-induction MRD (≥ 0.001)	3 (43)	2 (22)
End-induction MRD (≥ 0.0001)	4 (57)	5 (56)

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B acute lymphoblastic leukemia; CR, complete remission; DFCI, Dana-Farber Cancer Institute; ETP, early T-cell precursor; IF, induction failure; LL, lymphoblastic lymphoma; MRD, minimal residual disease; PCR, polymerase chain reaction; Ph+, Philadelphia chromosome-positive.

^aAmong those evaluable for induction events.

^bOn calaspargase arm, induction deaths include one T-immunophenotype (non-ETP) and one B-immunophenotype case; IF cases include four T-immunophenotype cases, two of which were ETP cases. On pegaspargase arm, IF case had B-immunophenotype.

^cAmong those who achieved CR.

^dAmong patients with B-ALL who achieved CR, with evaluable MRD samples; includes 152 samples tested by PCR assay and 11 by next-generation sequencing MRD assay.

^eAmong patients with T-ALL who achieved CR, with evaluable MRD samples.

TABLE A7. Baseline Characteristics and EFS of Children and Adolescents With Newly Diagnosed ALL or LL Treated on DFCI 11-001

Characteristic	n (%)	5-Year EFS % (± SE)	P
Overall	239	86.5 (± 2.3)	
Age at diagnosis, years			
< 10	179 (75)	87.8 (± 2.5)	.31
≥ 10	60 (25)	82.7 (± 5.0)	
Median (range)	5.2 (1.0-20.9)		
Sex			
Male	147 (62)	86.1 (± 2.9)	.70
Female	92 (38)	87.3 (± 3.6)	
Diagnosis			
ALL	230 (96)	86.4 (± 2.3)	.88
LL	9 (4)	88.9 (± 10.5)	
Immunophenotype			
B-immunophenotype	207 (87)	87.8 (± 2.4)	.074
T-immunophenotype ^a	32 (13)	78.1 (± 7.3)	
Initial DFCI risk group			
SR	141 (59)	91.2 (± 2.4)	.013
HR	98 (41)	79.8 (± 4.2)	
WBC at diagnosis, cells/ μ L ^b			
< 50,000	189 (82)	89.5 (± 2.3)	.003
≥ 50,000	41 (18)	72.0 (± 7.3)	
CNS status at diagnosis			
CNS 1	189 (79)	86.1 (± 2.6)	.75
CNS 2	34 (14)	85.1 (± 6.2)	
CNS 3	4 (2)	100 (NA)	
Traumatic with blasts	5 (2)	80.0 (± 17.9)	
Traumatic without blasts	7 (3)	100 (NA)	
Anterior mediastinal mass	19 (8)	78.9 (± 9.4)	.24
Cytogenetics, No. of evaluable	235 (98)		
<i>BCR-ABL1</i>	7 (3)	51.7 (± 18.7)	.007
Hyperdiploidy (51-65 chromosomes)	63 (26)	84.7 (± 4.7)	.64
Trisomies, chromosomes 4 and 10	39 (17)	86.0 (± 5.9)	.95
<i>ETV6-RUNX1</i> ^c	50 (21)	93.6 (± 3.6)	.11
Hypodiploidy (< 44 chromosomes)	1 (0.4)	100	—
<i>KMT2A</i> -rearranged	3 (1)	100	.53
iAMP21	11 (5)	80.8 (± 12.3)	.61
<i>TCF3-PBX1</i>	3 (1)	100 (NA)	.51
Normal karyotype	24 (10)	87.5 (± 6.8)	.96
Final DFCI risk group ^d			
SR	126 (55)	93.4 (± 2.3)	.12
HR	76 (33)	87.1 (± 4.1)	
VHR	21 (9)	80.7 (± 8.7)	

Abbreviations: ALL, acute lymphoblastic leukemia; CR, complete remission; DFCI, Dana-Farber Cancer Institute; DFS, disease-free survival; EFS, event-free survival; ETP, early T-cell precursor; HR, high risk; LL, lymphoblastic lymphoma; NA, not applicable; SR, standard risk; VHR, very high risk.

^aAmong T-immunophenotype cases, 5-year EFS for the 28 (12%) cases with non-ETP status was 82.1 (± 7.2) and for the 4 (2%) cases with ETP status was 50.0 (± 25.2).

^bWBC presented for patients with ALL.

^cIn exploratory analysis, there was no difference in 5-year EFS between treatment arms when *ETV6-RUNX1* cases were excluded ($P = .69$).

^dFinal DFCI risk group includes 223 non-Philadelphia chromosome-positive patients who achieved CR; DFS reported.

Protocol Redaction: DFCI ALL Consortium Protocol 11-001

Title: Randomized Study of Intravenous Calaspargase Pegol (SC-PEG asparaginase) and Intravenous Oncaspar in Children and Adolescents with Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

Principal Investigator: Lewis B. Silverman, MD

Coordinating Center: Dana-Farber Cancer Institute

Participating Sites:

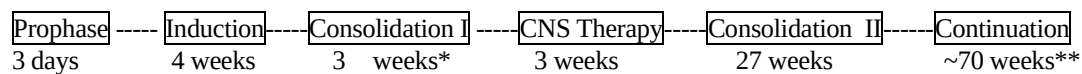
USA

- Columbia University Medical Center, Morgan Stanley Children's Hospital of New York-Presbyterian, New York, NY (Site PI: Kara Kelly, MD)
- Hasbro Children's Hospital, Providence, RI (Site PI: Jennifer Welch, MD)
- Inova Fairfax Hospital, Falls Church, VA (Site PI: Marshall Schorin, MD)
- Montefiore Medical Center, New York, New York (Site PI: Peter Cole, MD)
- San Jorge Children's Hospital, San Juan, Puerto Rico (Site PI: Luis Clavell, MD)

Canada

- CHU de Quebec, Quebec City, Quebec (PI : Bruno Michon, MD)
- CHU Sainte-Justine, University of Montreal, Montreal, Quebec (PI: Caroline Laverdiere, MD)
- McMaster University, Hamilton, Ontario (PI: Uma Athale, MD)

OVERALL TREATMENT SCHEMA



Randomization:

- A. IV SC-PEG x 1 dose during induction, then every 3-weeks x 10 doses (30 weeks total) beginning at start of CNS Therapy Phase***
- B. IV Oncaspar x 1 dose during induction, then every 2-weeks x 15 doses (30 weeks total) beginning at start of CNS Therapy Phase***

*~9 weeks for VHR patients

**Until 104 weeks (24 months) of CCR

***Post-induction Asparaginase begins during Consolidation I phase in VHR patients

1. OBJECTIVES

1.1 Study Design

A randomized study to determine the safety and feasibility of administering Calaspargase Pegol (SC-PEG asparaginase), a new formulation of PEG-asparaginase, compared with Oncaspar (the currently available form of PEG-asparaginase), in children and adolescents with newly diagnosed acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma treated with a DFCI ALL Consortium therapeutic backbone.

1.2 Primary Objectives

To assess the safety and feasibility associated with the administration of IV Calaspargase Pegol 2500 IU/m² given as a single dose during Remission Induction and every 3-weeks for 30 weeks during post-induction therapy in children and adolescents with newly diagnosed ALL

- 1.2.1 To assess the toxicity associated with IV Calaspargase Pegol administration and determine if it is significantly different than toxicity associated with IV Oncaspar.
- 1.2.2 To determine the serum asparaginase activity (SAA) levels associated with IV Calaspargase Pegol administered as a single dose during remission induction and every 3-weeks for 30 consecutive weeks during post-induction therapy, and to compare them to the SAA associated with IV Oncaspar administered as a single dose during Remission Induction and every 2-weeks for 30 consecutive weeks during post-induction therapy.

1.3 Secondary Objectives

- 1.3.1 To assess the frequency of bacteremia, fungemia and invasive fungal infections during the remission induction phase in patients receiving antibiotic prophylaxis.
- 1.3.2 To describe the outcome of children and adolescents with lymphoblastic lymphoma treated with a DFCI ALL Consortium treatment regimen.
- 1.3.3 To explore the impact on outcome of changing therapy for very high risk patients, defined as: i) B-precursor ALL patients with high end-induction minimal residual disease (MRD); patients with MLL-gene rearrangements or low hypodiploidy; or iii) T-ALL/lymphoblastic lymphoma patients with ETP phenotype.
- 1.3.4 To assess the feasibility of vitamin D screening and supplementation in children and adolescents undergoing treatment for ALL in the context of a multi-institutional trial.

- 1.3.4.1 To determine the prevalence of vitamin D deficiency in children and adolescents with ALL at the following time-points: at diagnosis, at the end of remission induction, at the start of continuation, and at the conclusion of therapy.
- 1.3.4.2 To assess the feasibility of correcting vitamin D deficiency with supplementation of vitamin D and calcium in patients found to have vitamin D deficiency.
- 1.3.4.3 To explore the relationship between vitamin D status and skeletal toxicity (fracture and osteonecrosis) in children and adolescents undergoing therapy for ALL.
- 1.3.4.4 To explore risk factors for vitamin D deficiency, including demographic variables such as age, sex, and ethnicity, as well as geographic location (geographic latitude) and season of measurement.
- 1.3.5 To determine the feasibility of prospective screening for absence of biallelic TCR γ deletions (ABGD) via qPCR in patients with T-ALL
 - 1.3.5.1 To determine the frequency of ABGD in patients with T-cell ALL at diagnosis
 - 1.3.5.2 To explore the correlation between early T-cell precursor (ETP) phenotype and ABGD
- 1.3.6 To determine the feasibility of prospective screening for abnormalities (eg, mutations, deletions, rearrangements) of IKZF1, CRLF2 and JAK1/2 in patients with newly diagnosed B-ALL.
 - 1.3.6.1 To determine the frequency of these abnormalities in standard-risk and high-risk patients
 - 1.3.6.2 To explore the correlation between the presence of these abnormalities and end-induction MRD levels.
- 1.3.7 To explore the relationship between mitochondrial BCL-2 family preconditions and response to chemotherapy as measured by induction response, end-induction MRD level and event-free survival (EFS).
- 1.3.8 To obtain patient samples for the development of primary xenograft mouse models with the goal of identifying novel therapies for high-risk (including those with high end-induction MRD, T-ALL with ABGD) and relapsed patients.

2. PARTICIPANT SELECTION

2.1 Eligibility Criteria

Participants must meet the following criteria to be eligible to participate in the study:

2.1.1 **Confirmed diagnosis of acute lymphoblastic leukemia or lymphoblastic lymphoma**

2.1.1.1 **For acute lymphoblastic leukemia:** diagnosis should be made by bone marrow aspirate or biopsy demonstrating $\geq$ 30% involvement by lymphoblasts, with flow cytometry or immunohistochemistry confirming B-precursor or T-ALL phenotype. While myeloid co-expression on blasts determined to be primarily lymphoid is allowed, patients with leukemia of ambiguous lineage are not eligible.

2.1.1.1.1 For patients with circulating blasts in the peripheral blood, flow cytometry confirmation of B-precursor or T-ALL phenotype is sufficient for registration onto the study. Bone marrow aspirate and/or biopsy should be performed as soon as feasible, preferably prior to the initiation of any therapy.

2.1.1.1.2 Note: patients with mature B-cell (Burkitt's) ALL are excluded from study. Mature B-cell is defined by the presence of surface immunoglobulin and/or the t(8;14)(q24;q32), t(8;22), or t(2;8) translocation and/or *c-myc*-gene rearrangement by FISH or PCR.

2.1.1.2 **For lymphoblastic lymphoma:** diagnosis may be made by i) biopsy of involved site (eg, node, mediastinal mass), or ii) by cytology from pleural fluid or other fluid collection or iii) by marrow aspirate/biopsy demonstrating $<$ 30% involvement by lymphoblasts (confirmed by flow cytometry, immunohistochemistry, cytogenetics and/or FISH studies) in a patient with evidence of lymphomatous masses by radiographic studies. Note: marrow aspirate and/or biopsy must be performed in patients with lymphoblastic lymphoma prior to study entry to confirm that patient does not meet definition of ALL. In rare circumstances, lymphoblastic lymphoma patients may be registered prior to marrow aspirate/biopsy if it is felt that the procedure cannot be safely performed; permission in advance by principal investigator or designee is required.

2.1.2 Prior Therapy: No prior therapy is allowed except for the following:

- Corticosteroids: Short courses of corticosteroid (defined as ≤ 7 days of corticosteroids within the 4-weeks preceding registration) are allowed prior to registration. *Note*: If patient has received pre-treatment with corticosteroids, they should not receive steroid prophylaxis, but should be treated as specified in Section 4.7.
 - Participants who have been on corticosteroids chronically (defined as more than 7 days of corticosteroids within the 4-weeks preceding registration or more than 28 days of corticosteroids over the preceding 6 months) are not eligible.
- IT Cytarabine: A single dose of intrathecal cytarabine (at the time of the diagnostic lumbar puncture) is allowed prior to registration. If patient has received IT cytarabine prior to registration, Day 1 IT cytarabine should not be administered.
- Emergent Radiation Therapy: Emergent radiation to the mediastinum or other life-threatening masses is allowed prior to registration.

2.1.3 Age: 365 days to < 22 years.

2.1.4 Laboratory Criteria: Participants must have direct bilirubin < 1.4 mg/dL (23.9 micromoles/L) *Note*: A total bilirubin of <1.4 mg/dL (23.9 micromoles/L) is acceptable to meet this requirement

2.1.5 Ability of parent or guardian to understand and the willingness to sign a written informed consent document.

2.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for the study.

2.2.1 Participants who have received more than 7 days of corticosteroids in the preceding 4 weeks or more than 28 days of corticosteroids in the preceding 6 months are not eligible.

2.2.2 Participants who have received any chemotherapy or radiotherapy for previous malignancy are not eligible. Participants who have ever previously received any anti-neoplastic agent, including methotrexate, 6-mercaptopurine, 6-thioguanine, vincristine cyclophosphamide, cytarabine (except for IT cytarabine), or any anthracycline, for any reason (eg, rheumatologic or autoimmune condition) are not eligible.

2.2.3 Participants may not be receiving any other investigational agents.

2.2.4 Participants known to be HIV-positive are excluded (*Note*: HIV testing is not required prior to enrollment). HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for

pharmacokinetic interactions with Calaspargase Pegol (SC-PEG asparaginase). In addition, these individuals are at increased risk of lethal infections when treated with myelosuppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

- 2.2.5 Uncontrolled intercurrent illness including, but not limited to ongoing infection with vital sign instability (hypotension, respiratory insufficiency), life-threatening acute tumor lysis syndrome (eg, with renal failure), symptomatic congestive heart failure, cardiac arrhythmia, intracranial or other uncontrolled bleeding, or psychiatric illness/social situations that would limit compliance with study requirements.
- 2.2.6 Pregnant women are excluded from this study because many of the agents used on this protocol have potential for teratogenic and/or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with these chemotherapy agents, breastfeeding should be discontinued if the mother is enrolled.
- 2.2.7 Individuals with a history of a previous malignancy are ineligible because cases of secondary leukemia/lymphoma arising after a previous malignancy are biologically distinctive and may require different therapies. Also, exposure to previous anti-neoplastic treatment may alter the ability to tolerate or respond to the agents utilized in this protocol. Exception: Individuals with a previous malignancy treated with surgery only (no chemotherapy or radiotherapy) more than 5 years prior to registration may be enrolled.

2.3 **Inclusion of Women, Minorities and Other Underrepresented Populations**

Individuals of both genders and all racial and ethnic backgrounds are eligible for this study.

3. RISK GROUP CLASSIFICATION

3.1 **Risk Group Definitions**

3.1.1 **Standard Risk: All of the criteria must be met:**

- Age: 365 days to < 10 years.
- WBC count: Highest pre-treatment WBC <50,000/mm³ (prior to registration).
- CNS leukemia: No evidence of CNS leukemia by morphology, defined by meeting all of the following criteria:
 1. Diagnostic lumbar puncture (Day 1) without any CSF blast cells on cytospin (CNS-1) or fewer than 5 WBC/hpf in CSF with blast cells noted on cytospin (CNS-2). If traumatic tap (>10 RBC's on CSF cell count) with ≥ 5 WBC cells are seen, use Steinherz/Bleyer algorithm (see 5.1.6) to determine if patients should be considered CNS-2 or CNS-3 for purposes of risk group assignment.
 2. CNS-1 CSF on Days 18 and 32. SR patients with CNS-2 CSF on Days 18 or 32 will be re-classified and re-consented as high risk. SR patients with CNS-3 CSF (≥ 5 WBC/hpf with blast cells) on Day 18 will be re-classified and re-consented as high risk and on Day 32 will be considered Induction Failure. If traumatic tap (>10 RBC's on CSF cell count) with ≥ 5 WBC cells are seen, use Steinherz/Bleyer algorithm to determine if patients should be considered CNS-2 or CNS-3 for purposes of risk group assignment.
 3. Absence of a cranial nerve palsy at diagnosis.
- Immunophenotype: Predominance of B-precursor cell surface antigens on lymphoblasts.
- Chromosomal abnormalities: Absence of t(9;22), MLL gene translocations and hypodiploidy < 44 chromosomes as determined by karyotype, PCR or FISH analysis. If chromosomal data unavailable, may continue to be treated as SR if all other risk group criteria are met.
- MRD (leukemia patients only): MRD level < 0.001 on a marrow sample obtained at end of remission induction therapy (Day 32). SR patients with MRD levels ≥ 0.001 at the end of remission induction therapy (Day 32) will be re-classified and re-consented as very high risk, and very high risk treatment will commence with Consolidation IB. SR patients whose end-of-induction MRD status cannot be determined will remain SR.

3.1.2 **High Risk: Any one of the following criteria (except patients who meet any VHR criteria)**

- Age: 10 to < 22 years
- WBC count: Highest pre-treatment WBC $\geq 50,000/\text{mm}^3$ (prior to registration).
- CNS leukemia: Evidence of CNS leukemia by morphology, defined by meeting any of the following criteria:

1. Diagnostic lumbar puncture (Day 1) with 5 or greater WBC/hpf and blast cells on cytospin (CNS-3). If traumatic tap (>10 RBC's on CSF cell count) with ≥ 5 WBC cells are seen, use Steinherz/Bleyer algorithm (see 5.1.6) to determine if patients should be considered CNS-2 or CNS-3 for purposes of risk group assignment.
 2. CNS-2 on Day 18 or 32. Patients with CNS-2 CSF (fewer than 5 WBC per hpf in CSF, with blasts cells on cytospin) on Day 18 or 32 will be re-consented as high risk if otherwise considered standard risk.
 3. CNS-3 on Day 18. Patients with CNS-3 CSF (≥ 5 WBC/hpf with blast cells) on Day 18 will be re-consented as high risk if previously considered standard risk. If traumatic tap (>10 RBC's on CSF cell count) with ≥ 5 WBC cells are seen, use Steinherz/Bleyer algorithm (see 5.1.6) to determine if patients should be considered CNS-2 or CNS-3 for purposes of risk group assignment.
 4. Presence of a cranial nerve palsy at diagnosis.
- Immunophenotype: Predominance of T-cell markers on lymphoblasts. Note: T-ALL and T-lymphoblastic lymphoma patients with immunophenotype consistent with early T-cell precursor (ETP) as determined by DFCI/CH central review will be considered VHR.
 - MRD (leukemia patients only): B-precursor HR patients with MRD level < 0.001 on a marrow sample obtained at end of remission induction therapy (Day 32) will continue to be treated as HR. B-precursor HR patients with MRD levels ≥ 0.001 at the end of remission induction therapy (Day 32) will be re-classified and re-consented as very high risk, and very high risk treatment will commence with Consolidation IB. HR patients whose end-of-induction MRD status cannot be determined will remain HR. MRD will not be used to change risk group of T-lineage patients.

3.1.3 **Very High Risk: Any of the following criteria**

- Chromosomal abnormalities:
 - Presence of MLL gene translocations [such as t(4;11)] by karyotype or FISH or molecular analyses.
 - Presence of hypodiploidy < 44 chromosomes by karyotype or FISH analysis.
- ETP phenotype: For T-ALL/lymphoblastic lymphoma patients, presence of early T-cell precursor phenotype (ETP) as determined by DFCI/CH central review
- MRD status (leukemia patients only): B-precursor patients previously considered either standard or high risk with MRD ≥ 0.001 at end of remission induction therapy (Day 32).
- Patients who meet very high risk criteria will be re-consented as Very High Risk (VHR) if previously considered standard risk or high risk, and will commence with VHR treatment at the start of Consolidation IB.

3.1.4 **Special Situation: t(9;22)**

Patients found to have t(9;22) by cytogenetics, FISH and/or PCR will be removed from study by Day 15. These patients will be eligible to enroll on the open COG Protocol for Philadelphia chromosome-positive ALL.

3.1.5 **Lymphoblastic Lymphoma:** Lymphoblastic Lymphoma patients should be treated as Standard Risk, High Risk or Very High Risk based on age, immunophenotype, CNS status and cytogenetics, as specified above. MRD will not be used in lymphoblastic lymphoma for risk-group classification.

3.1.6 **Steinherz/Bleyer Algorithm to Interpret Traumatic LP's (>10 RBC per high power field) with ≥ 5 WBC/hpf:**

CSF specimens with > 10 RBC/hpf and ≥ 5 WBC/hpf should be treated as CNS-3 if: $(\text{CSF WBC}/\text{CSF RBC}) > 2 \times (\text{Blood WBC}/\text{Blood RBC})$.

All other CSF specimens with > 10 RBC/hpf and ≥ 5 WBC/hpf in CSF specimen should be treated as CNS2.

3.2 **Determination of Final Risk Group Status for patients with ALL**

- Patients should begin treatment as per appropriate risk group based on available data at the time of diagnosis (eg, age, presenting leukocyte count, immunophenotype, CNS status)
- Final risk group classification may differ from initial risk group based on results obtained during and immediately after remission induction therapy, based on:
 - a) Presence of CNS blasts at Day 18 or 32
 - b) Presence of MLL gene translocation or hypodiploidy (< 44 chromosomes) determined by karyotype, FISH or other molecular studies: all patients re-classified as VHR regardless of initial risk group classification. It is expected that re-classified patients will be able to begin VHR treatment at the end of remission induction treatment (beginning of Consolidation I)
 - c) Presence of early T-cell precursor phenotype (ETP) in T-ALL patients as determined by DFCI/CH central review. It is expected that re-classified ETP patients will be able to begin VHR treatment at the end of remission induction treatment (beginning of Consolidation I).
Note: See Section for reclassification of lymphoblastic lymphoma patients.
 - d) MRD level at end of remission induction therapy.
 - i) SR patients: If $\text{MRD} \geq 0.001$, will be re-classified as VHR, and begin VHR treatment at the start of the second cycle of Consolidation I therapy (Consolidation IB).
 - ii) HR B-lineage patients: If $\text{MRD} \geq 0.001$, will be re-classified as VHR and begin VHR treatment at the start of the second cycle of Consolidation I therapy (Consolidation IB).
 - iii) MRD will not be used to change risk group classification of T-cell patients

If end-of-induction MRD status cannot be determined, then patient will continue to be treated per initial risk group classification

4. TREATMENT PLAN

Participants should begin treatment as soon as feasible after registration. Active issues related to fever, anemia, thrombocytopenia, coagulopathy, and acute tumor lysis syndrome should be addressed prior to the initiation of leukemia-directed therapy whenever possible. See Section for Supportive Care Guidelines.

Participants will receive the following phases of treatment:

- Steroid Prophase (3 days)
- Remission Induction (29days)
- Consolidation I (3 weeks for SR/HR patients, 9 weeks for VHR patients)
- CNS Phase (3 weeks)
- Consolidation II (27 weeks)
- Continuation (until 24 months in complete continuous remission).

Additionally, all outpatient chemotherapy for each cycle must be prescribed by a physician, nurse practitioner or physician assistant, as per institutional standard, on the day that the patient is evaluated and found to meet criteria for that cycle. This means that only one cycle of outpatient chemotherapy may be prescribed at each visit, and refills for chemotherapy prescriptions are not allowed for study patients. Exception can be made for patients receiving Purixan® (6-MP oral suspension) who must be dispensed full bottles per medical insurance restrictions; in these cases, medical staff should review dosing with patient/family at the start of each cycle. Under no circumstances may other clinical staff call in prescriptions for chemotherapy for patients on study.

4.1 STEROID PROPHASE (All patients)

4.1.1 Starting Time: After confirmation of diagnosis, informed consent signed and patient registered

4.1.2 Starting Criteria: All patients who are eligible and enrolled on study should begin treatment with this phase, with the following exception: patients who have already received steroid pre-treatment prior to beginning protocol therapy (See Section for allowable steroid pre-treatment). Such patients should undergo lumbar puncture with intrathecal cytarabine, and then proceed directly to Remission Induction Phase (Section for Standard Risk and Section for High Risk and Very High Risk).

4.1.3 Steroid Prophase Therapy

Day	1	2	3
	P	P	P
	IT Ara		

***Perform Therapeutic Lumbar Puncture on Day 1. Send CSF for cell count with differential and/or cytology.**

***Complete blood count with differential must be performed at diagnosis and after completion of 3 full days of methylprednisolone (Day 4). *Absolute blast count must be calculated at diagnosis and at Day 4 (Absolute blast count = peripheral blood WBC x % blasts)**

***All leukemia patients should have bone marrow and peripheral blood sample sent to develop MRD probe prior to starting systemic therapy (steroid prophase).**

***Note: Antibiotic Prophylaxis should begin during the Prophase in all afebrile patients and continue until count recovery after expected hematologic nadir (ANC ≥ 200 or APC $\geq 500/\text{mm}^3$).**

4.1.4 Steroid Prophase Dosages, Schedules & Routes

- P** Methylprednisolone 32 mg/m²/day IV divided every 8 hours (or three times per day) on days 1-3.

Note: Only IV Methylprednisolone should be administered during Prophase. Administration of oral prednisone (40 mg/m²/day divided into three daily doses) instead of intravenous methylprednisolone during prophase is not allowed, except if discussed in advance with Principal Investigator.

ITArA Intrathecal Cytarabine given on Day 1, dosed by age:

Age	1 – 1.99 yrs	2 - 2.99yrs	≥3 yrs
Cytarabine	20 mg	30 mg	40 mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

4.2 Additional Lumbar Punctures for Patients with CNS Leukemia

- 4.2.1 CNS blasts on Initial Lumbar Puncture (LP): Patients with CNS leukemia (CNS-2, CNS-3 or traumatic LP with blasts; regardless of RBC count) on initial Lumbar puncture (day 1) will receive additional IT Cytarabine (beginning on Days 4-6) twice-weekly until the CSF is clear, and then two additional doses will be given.

Dose of IT cytarabine according to age as indicated above.

Note: 2 additional doses of IT chemotherapy (with clear CSF—no blasts) should be administered after first clear Lumbar Puncture. If patients are still receiving twice weekly lumbar punctures with IT therapy at Day 18, IT chemotherapy should be changed from IT cytarabine to IT Methotrexate/Cytarabine/Hydrocortisone on Day 18 and IT Methotrexate/Cytarabine/Hydrocortisone should be used for all subsequent lumbar punctures with IT therapy after Day 18, if any are still necessary (except if mucositis present, in which case IT Methotrexate may be held).

4.3 Antibiotic Prophylaxis during Remission Induction Phase

Antibiotic prophylaxis with a fluoroquinolone antibiotic (either levofloxacin or moxifloxacin) will be initiated during the Steroid Prophase and continue throughout the Remission Induction phase until count recovery after expected hematologic nadir ($ANC \geq 200$ or $APC \geq 500/mm^3$). Patients unable to tolerate fluoroquinolones due to allergy or other toxicity should receive intravenous cefepime as prophylaxis. If a patient is unable to tolerate fluoroquinolone or cefepime, contact Principal Investigator.

Patients receiving broad-spectrum antibiotics for fever or documented infection may discontinue prophylactic antibiotics. Broad spectrum antibiotics for febrile neutropenia should be continued until $ANC > 500/mm^3$, or per institutional guidelines.

Because of the high risk of infection, treatment should begin on an inpatient basis and hospitalization of participants is encouraged throughout the induction phase. Outpatient treatment during the induction phase may be considered after recovery of the absolute neutrophil count (ANC) after the expected hematologic nadir.

4.4 REMISSION INDUCTION PHASE (STANDARD RISK PATIENTS)

4.4.1 Remission Induction Phase for SR Patients

Day	4	5	6	7...	11 ...	18*...	25...		32 ⁺
P	→	→	→		→	→	→	→ →	begin taper
V					V	V	V		
D	D								
			m						
				ASP		IT MAH		ITM	

***On Day 18, perform marrow aspirate (only in leukemia patients who have consented to optional Day 18 bone marrow procedure) and therapeutic lumbar puncture with intrathecal chemotherapy (all patients). Collect Day 18 blood only if patients consented to additional research peripheral blood samples.**

⁺ On Day 32, perform marrow aspirate/biopsy (if marrow involvement at diagnosis) and therapeutic lumbar puncture with intrathecal chemotherapy. It is suggested that the marrow sample be sent for cytogenetics/FISH (if abnormal at diagnosis).

+For Leukemia Patients: Day 32 Marrow sample must be sent for MRD analysis to determine final risk group assignment.

See 6.8.3 if peripheral blood criteria for remission are not met by Day 32.

***Note: Antibiotic Prophylaxis should begin during the Prophase and continue through the Induction phase in all afebrile patients until count recovery after expected hematologic nadir ($ANC \geq 200$ or $APC \geq 500/mm^3$).**

See Section for dose modifications. See Section for allowable deviations in timing of medications/procedures and for allowable variation in dosing.

4.4.2 Starting Time: After completion of steroid prophase

4.4.3 Starting Criteria:

- Direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L) If direct bilirubin > 1.4 mg/dL (23.9 micromoles/L), go to Section, "Special Circumstance 1: Hyperbilirubinemia"

4.4.4 Dosages, Schedules & Routes

P Prednisone Prednisone or Prednisolone 40 mg/m²/day orally divided into two or three doses per day or methylprednisolone (solumedrol) 32 mg/m²/day IV divided every 8 hours (or three times per day) on Days 4-32.

Note: A steroid taper (consisting of either prednisone or methylprednisolone) should be administered after completion of Induction course of prednisone/methylprednisolone. Steroid taper should commence: 1) after

completion of end-induction restaging procedures (marrow and/or scans) as long as the results of these studies are consistent with complete remission (including peripheral blood count recovery) and patient will be proceeding to Consolidation I phase, or 2) after last dose of steroid on Day 32, whichever comes first. Full-dose prednisone (40 mg/m²/day, or its methylprednisolone equivalent) should not be administered after Day 32. Duration of corticosteroid taper is up to discretion of treating physician but should not exceed 7 days (i.e., all corticosteroid should be completed by Day 39).

- | | | |
|-----|--|--|
| V | Vincristine | 1.5 mg/m ² (maximum dose 2 mg) IV push or IV via minibag every week x 4 (on Days 4, 11, 18 and 25). |
| D | Doxorubicin | <p>Doxorubicin 30 mg/m² IV on Days 4 and 5.</p> <ul style="list-style-type: none"> • Give as IV push via CVL or via freshly placed peripheral IV. • May give as IV bolus over 15 minutes if administered via a central line. • <u>No</u> Dexrazoxane |
| m | Methotrexate | <p>Methotrexate 40 mg/m² IV push on Day 6. Give at least 8 hours but not more than 24 hours, after last Doxorubicin dose.</p> <p><u>Note:</u> Do not give methotrexate if effusions or ascites are present, or if creatinine is beyond upper limits normal for age. .</p> |
| ASP | Asparaginase according to randomization. Give on Day 7. Mix in 100 mL Normal Saline and give IV over 1 hour. | |
| | | <p>A. SC-PEG Asparaginase (Calaspargase Pegol) 2500 IU/m²/dose IV x 1 dose, <u>or</u></p> <p>B. Oncaspar 2500 IU/m²/dose IV x 1 dose.</p> |

IT MAH Intrathecal Methotrexate/Cytarabine/Hydrocortisone
Give on Day 18. Dose according to age:

Age	1 – 1.99 yrs	2 - 2.99yrs	≥3yrs
Methotrexate	8mg	10mg	12mg
Cytarabine	20mg	30mg	40mg
Hydrocortisone	9mg	12mg	15mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

ITM Intrathecal Methotrexate on Day 32. If peripheral blood criteria for remission are met, perform bone marrow aspirate and lumbar puncture. Administer intrathecal methotrexate medications according to age:

Age	1 - 1.99yrs	2 - 2.99yrs	≥ 3yrs
Methotrexate	8mg	10mg	12mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

4.5 REMISSION INDUCTION PHASE (HIGH RISK AND VERY HIGH RISK PATIENTS)

4.5.1 Remission Induction Phase for HR/VHR patients

Day	4	5	6	7...		11 ...	18*...		25...		32 ⁺
P	→	→	→	→	→	→	→		→	→	begin taper
V						V	V		V		
Dd	Dd										
			m								
			ASP								
						IT MAH					
										ITM	

***On Day 18, perform marrow aspirate (only in leukemia patients who have consented to optional Day 18 bone marrow procedure) and therapeutic lumbar puncture with intrathecal chemotherapy (all patients). Collect Day 18 blood only if patients consented to additional research peripheral blood samples. + On Day 32, perform marrow aspirate/biopsy (if marrow involvement at diagnosis) and therapeutic lumbar puncture with intrathecal chemotherapy. It is suggested that the marrow sample be sent for cytogenetics/FISH (if abnormal at diagnosis).**

+For Leukemia Patients: Day 32 Marrow sample must be sent for MRD analysis to determine final risk group assignment

See 6.8.3 if peripheral blood criteria for remission are not met by Day 32.

***Note: Antibiotic Prophylaxis should begin during the Prophase and continue through the Induction phase in all afebrile patients until count recovery after expected hematologic nadir ($ANC \geq 200$ or $APC \geq 500/mm^3$).**

See Section for dose modifications. See Section for allowable deviations in timing of medications/procedures and for allowable variation in dosing.

4.5.2 Starting Time: After completion of steroid prophase

4.5.3 Starting Criteria:

- Direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L). If direct bilirubin > 1.4 mg/dL (23.9 micromoles/L), go to Section, "Special Circumstance 1: Hyperbilirubinemia"

P Prednisone Prednisone or Prednisolone 40 mg/m²/day orally divided into two or three doses per day or methylprednisolone (solumedrol) 32 mg/m²/day IV divided every 8 hours (or three times per day) on Days 4-32.

Note: A steroid taper (consisting of either prednisone or methylprednisolone) should be administered after completion of Induction course of prednisone/methylprednisolone. Steroid taper should commence: 1) after completion of end-induction restaging procedures (marrow and/or scans) as long as the results of these studies are consistent with complete remission (including

peripheral blood count recovery) and patient will be proceeding to Consolidation I phase, or 2) after last dose of steroid on Day 32, whichever comes first. Full-dose prednisone (40 mg/m²/day, or its methylprednisolone equivalent) should not be administered after Day 32. Duration of corticosteroid taper is up to discretion of treating physician but should not exceed 7 days (i.e., all corticosteroid should be completed by Day 39).

- | | | |
|-----|---|--|
| V | Vincristine | 1.5 mg/m ² (maximum dose 2 mg) IV push or IV via minibag every week x 4 (on Days 4, 11, 18 and 25). |
| D | Doxorubicin | <p>30 mg/m² IV preceded by Dexrazoxane 300 mg/m² IV on day 4 and day 5. Suggested administration for both drugs:</p> <ul style="list-style-type: none"> • Minute 0 Dexrazoxane over 15 minutes • Minute 15 Doxorubicin IV push via central line or freshly placed peripheral IV. May give doxorubicin IV over 15 minutes if given via central venous line. • Goal is no more than 30 minutes maximum elapsed administration time combined for both drugs • May give doxorubicin prior to dexrazoxane if given via peripheral IV. |
| m | Methotrexate | <p>Methotrexate 40 mg/m² IV push on Day 6. Give at least 8 hours but not more than 24 hours, after last Doxorubicin dose.</p> <p><u>Note:</u> Do not give methotrexate if effusions or ascites are present, or if creatinine is beyond upper limits normal for age.</p> |
| ASP | <p>Asparaginase according to randomization. Give on Day 7. Mix in 100 mL Normal Saline and give IV over 1 hour.</p> <p style="margin-left: 40px;">A. SC-PEG Asparaginase (Calaspargase Pegol) 2500 IU/m²/dose IV x 1 dose, <u>or</u></p> <p style="margin-left: 40px;">B. Oncaspar 2500 IU/m²/dose IV x 1 dose.</p> | |

IT MAH Intrathecal Methotrexate/Cytarabine/Hydrocortisone
Give on Day 18. Dose according to age:

Age	1 – 1.99 yrs	2 - 2.99yrs	≥3yrs
Methotrexate	8mg	10mg	12mg
Cytarabine	20mg	30mg	40mg
Hydrocortisone	9mg	12mg	15mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

ITM Intrathecal Methotrexate on Day 32. If peripheral blood criteria for remission are met, perform bone marrow aspirate and lumbar puncture. Administer intrathecal methotrexate medications according to age:

Age	1 - 1.99yrs	2 - 2.99yrs	≥ 3yrs
Methotrexate	8mg	10mg	12mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

4.6 Special circumstance: Induction Therapy for Patients with Hyperbilirubinemia on Day 4

If direct bilirubin >1.4 mg/dl (23.9 micromoles/L), on Day 4, timing of chemotherapy is as follows:

Prednisone	Give Days 4 through 32
Vincristine	Give Days 4, 11 18 and 25 if direct bilirubin $\leq$ 3.0 mg/dL (51.3 micromoles/L). If direct bilirubin is > 3.0 mg/dL (51.3 micromoles/L), hold dose of vincristine. With a bilirubin at this level, it may be allowable under certain circumstances to administer vincristine at 50% dose but only with prior approval of Principal Investigator.
Doxorubicin	Hold until direct bilirubin $\leq$ 1.4 mg/dL (23.9 micromoles/L), then give (according to risk group status) on 2 consecutive days. HR/VHR should receive Dexrazoxane with doxorubicin. If patient has not received doxorubicin because direct bilirubin is not $\leq$ 1.4 mg/dL (23.9 micromoles/L), by Day 18 patient should be removed from study.
Methotrexate	Hold until direct bilirubin $\leq$ 1.4 mg/dL, then give 8-24 hours after 2 nd dose of doxorubicin.
Asparaginase	Hold until direct bilirubin is $\leq$ 1.4 mg/dL (23.9 micromoles/L) ; Give 1 day after methotrexate dose is given.
IT MAH	Administer on Day 18. Hold intrathecal methotrexate if direct bilirubin still > 1.4 mg/dL (23.9 micromoles/L), at that time.

Day 18 bone marrow aspirate should not be performed if any agents were delayed due to hyperbilirubinemia.

Perform marrow aspirate/biopsy (if marrow involvement at diagnosis) and therapeutic lumbar puncture (with intrathecal chemotherapy) at end of remission induction therapy when peripheral blood counts recover, at least 3 weeks from doxorubicin. It is suggested that the marrow sample be sent for cytogenetics/FISH (if abnormal at diagnosis).

For ALL patients: Day 32 Marrow sample must be sent for MRD analysis to determine final risk group assignment.

Note: If direct bilirubin remains persistently elevated above 1.4 mg/dL (23.9 micromoles/L) at Day 18, then participant should be removed from study.

4.7 Special circumstance: Induction Therapy for Patients treated without Steroid Prophase

First day of chemo = Day 4. Treat without Steroid Prophase.

Prednisone	Give Days 4 through 32.
Vincristine	Give Days 4, 11, 18 and 25
Doxorubicin	Give on Days 4 and 5 according to risk group. Dexrazoxane given to HR/VHR patients.
Methotrexate	Give on Day 6.
Asparaginase	Give on Day 7, according to randomization.
IT cytarabine	Administer on Day 4.
IT methotrexate/cytarabine/hydrocortisone:	Administer on Day 18
IT methotrexate	Administer on Day 32, if peripheral blood criteria for remission all met.

On Day 18, perform therapeutic lumbar puncture (with intrathecal chemotherapy). Leukemia patients who have consented to Day 18 marrow should have this procedure performed at the same time as therapeutic lumbar puncture.

On Day 32, perform marrow aspirate/biopsy (if marrow involvement at diagnosis) and therapeutic lumbar puncture with intrathecal chemotherapy. It is suggested that the marrow sample be sent for cytogenetics/FISH (if abnormal at diagnosis).

For Leukemia Patients: Day 32 Marrow sample must be sent for MRD analysis to determine final risk group assignment.

4.8 **COMPLETION OF REMISSION INDUCTION THERAPY**

4.8.1 **Complete remission definition:**

Leukemia: An interpretable bone marrow (a specimen with normal marrow elements present) with fewer than 1% malignant lymphoblasts by microscopic examination and peripheral blood without lymphoblasts, and an $APC \geq 1000/mm^3$ and platelets $\geq 100,000/mm^3$, and no evidence of extramedullary leukemia (no blasts in spinal fluid, at least 70% reduction in size of masses noted on imaging at diagnosis, as defined below for patients with lymphoblastic lymphoma). Note: Patients are allowed to have $\geq 1\%$ normal myeloid or lymphoid blasts (hematogones) in their marrow consistent with recovery and still meet the definition of complete remission. Normal recovery blasts may be distinguished from persistent malignant lymphoblasts by flow cytometry, immunohistochemistry or other studies. Consult principal investigator with any questions.

Lymphoblastic Lymphoma: At least a 70% reduction in size of largest nodes or masses noted at diagnosis. Reduction may be measured as a decrease in a sum of the products of the two greatest diameters (SPD) of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features:

- a) they should be clearly measurable in at least two perpendicular dimensions,
- b) they should include mediastinal masses whenever this site was initially involved.

In addition to this radiographic criterion, there should also be complete disappearance of all clinical evidence of disease by physical examination and no evidence of disease in spinal fluid or in bone marrow (if involved at initial diagnosis). Definition of marrow remission for lymphoblastic lymphoma patients with initial marrow involvement is the same as that used for patients with leukemia (above).

When patient is documented to be in complete remission, proceed to Consolidation I.

4.8.2 **Timing of Bone Marrow Examination and Therapeutic Lumbar Puncture**

Leukemia patients and Lymphoblastic Lymphoma patients with marrow involvement at diagnosis: Bone marrow aspirate/biopsy should be performed on (or as close as possible) to Day 32 of remission induction, regardless of blood counts. Sample for MRD analysis should be sent for all leukemia patients. Therapeutic lumbar puncture (with intrathecal methotrexate) may be performed at the same time as this marrow aspirate/biopsy only if peripheral blood counts meet criteria for complete remission ($APC \geq 1000/mm^3$ and platelets $\geq 100,000/mm^3$) and there is no evidence of extramedullary leukemia. If patient is in documented complete remission on Day 32, proceed to Consolidation I.

Note: For patients with leukemia, it is essential that bone marrow sample for MRD analysis be sent at Day 32.

Lymphoblastic Lymphoma patients without marrow involvement at diagnosis: Marrow aspirate/biopsy is not required at Day 32, but should be considered if there is delayed count recovery. Therapeutic lumbar puncture (with intrathecal methotrexate) should be performed at Day 32 (or as close as possible to this date) only if peripheral blood counts meet criteria for

complete remission ($\text{APC} \geq 1000/\text{mm}^3$ and platelets $\geq 100,000/\text{mm}^3$) and there is no evidence of extramedullary leukemia.

4.8.3 **Delayed Recovery:**

If complete remission is NOT achieved on Day 32 because either a) patient does not meet peripheral blood criteria, or b) marrow is too hypocellular to interpret (not enough marrow cells to perform adequate marrow differential), and $<5\%$ lymphoblasts are identified in the marrow (leukemia patients and lymphoblastic lymphoma patients with initial marrow involvement):

4.8.3.1 Patient does not meet peripheral blood criteria:

- 1) For leukemia patients and lymphoblastic lymphoma patients with initial marrow involvement: **perform bone marrow aspirate and biopsy on Day 32.** Day 32 marrow aspirate from leukemia patients should be sent for MRD testing, regardless of peripheral blood counts. Repeat marrow aspirate when peripheral blood counts meet criteria for remission, or by Day 53 if counts still not recovered. Additional bone marrow aspirates/biopsies may be performed between Days 32-53 at discretion of treating physician. For leukemia patients, send specimen from any bone marrow performed for MRD analysis, if possible.
- 2) **Do Not perform lumbar puncture. Administer vincristine 1.5 mg/m² (maximum dose 2 mg) IV push or IV via minibag weekly until CR is achieved.** When peripheral blood criteria met, lumbar puncture with intrathecal methotrexate should be performed (may be performed at same time as bone marrow aspirate for leukemia patients and lymphoblastic lymphoma patients with initial marrow involvement).
- 3) Patient will be removed from study if counts do not recover by Day 53

4.8.3.2 Hypocellular marrow (peripheral blood criteria met but marrow uninterpretable)--Leukemia patients and Lymphoblastic Lymphoma patients with initial marrow involvement only:

- 1) Continue vincristine 1.5 mg/m² (maximum dose 2 mg) IV push or IV via minibag weekly on Days 32, 39 and 46 or until CR achieved, whichever comes first.
- 2) Repeat marrow aspirate and/or biopsy weekly until complete remission is documented.
- 3) Complete remission must be documented by Day 53 for patients to remain on study.

4.8.4 **Induction Failure**

Leukemia: If $\geq 1\%$ blasts (confirmed to be leukemic lymphoblasts by flow cytometry, immunohistochemistry or other studies) are identified in the marrow on Days 32, or on any marrow performed up through Day 53 (without a preceding marrow consistent with complete

remission), the patient will be classified as an Induction Failure and removed from protocol (contact Principal Investigator or designee prior to removing from protocol if patient is induction failure). Any patient with evidence of extramedullary leukemia on exam, in the spinal fluid or by radiographic imaging (<70% reduction in size of largest nodes or masses noted at diagnosis, or any new biopsy-proven masses) will also be considered an induction failure, regardless of marrow findings.

Lymphoblastic Lymphoma: If end-induction imaging reveals persistent nodal involvement or masses (< 70% reduction in size of largest nodes or masses noted at diagnosis), the patient will be classified as an Induction Failure and removed from protocol (call Principal Investigator or designee if patient is an induction failure). Any patient with new, biopsy-proven sites of disease will also be considered an induction failure. In addition, any patient with evidence of persistent disease in bone marrow (confirmed by flow cytometry, FISH or other studies) or spinal fluid will also be considered an induction failure.

4.8.5 **Indeterminate marrow**

If $\geq 5\%$ blasts that are not clearly lymphoblasts based on morphology are identified in the marrow on Day 32 (or any marrow performed through Day 53), try to better characterize blasts by flow cytometry, FISH, immunohistochemistry or other studies. Repeat marrows can be performed weekly for questionable cases. Vincristine should be given if decision is made to repeat marrow in one week at a dose of $1.5 \text{ mg/m}^2/\text{week}$ (maximum dose 2 mg) IV push or IV via minibag. If marrow results are indeterminate, call Principal Investigator or designee to discuss management.

4.8.6 **CNS blasts at the end of induction:**

If patient with ≥ 5 WBC/hpf in CSF with blast cells seen on cytospin (CNS-3) from lumbar puncture performed at end of induction (on Days 32, or after if delayed recovery), patient is considered Induction Failure, and is removed from protocol.

If patient has had CNS blasts present throughout Induction Therapy (CNS-2 or 3) without clearance of CSF, and blasts persist at Day 32, then patient is considered an Induction Failure at that time, and is removed from protocol. Note: If Day 32 lumbar puncture is clear of blasts, patient is not considered Induction Failure, even if patient has not yet had 3 negative lumbar punctures in a row by that time point.

If blasts are identified in the CSF from lumbar puncture performed at end of induction but CSF WBC < 5 cells/hpf (CNS-2) in a patient otherwise with previously clear CSF (no lymphoblasts) and in peripheral blood and bone marrow remission:

- SR patient reclassified to HR, and will be considered CNS-positive (to receive 1800 cGy during CNS Intensification Phase)
- If HR, will receive 1800 cGy during CNS Intensification Phase, regardless of prior radiation assignment.
- Twice-weekly lumbar punctures with intrathecal methotrexate, cytarabine and hydrocortisone. Continue twice weekly lumbar punctures until CSF is clear, and then two additional doses will be given.

- Do not proceed to Consolidation I Phase. Instead, administer the following systemic chemotherapy (one cycle only):
 - 1) Vincristine 1.5 mg/m² (maximum dose 2 mg) IV push weekly or IV via minibag.
 - 2) Doxorubicin 30 mg/m² and dexrazoxane 300 mg/m².
 - 3) 6-mercaptopurine 50 mg/m²/day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount.
- If blasts have cleared by Day 53 patient should proceed to next phase of treatment (Consolidation I) when starting criteria for that phase are met.
- If patient with new CNS-2 status at Day 32 has persistent CNS blasts at Day 53 (regardless of CSF cell count), the patient will be classified as an Induction Failure and will be removed from protocol

If patient has scan evidence of CNS disease (eg, leukemic infiltrate of cranial nerve) at end of remission induction, then the patient will be considered an Induction Failure and be removed from protocol.

4.9 CONSOLIDATION I PHASE: STANDARD RISK PATIENTS

4.9.1 Starting Time: Patients must be in documented remission at all sites.

4.9.2 Starting Criteria: $APC \geq 1,000$, platelets $\geq 100,000$, direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L), SGOT ≤ 8 x normal, creatinine normal for age, no mucositis, no ascites/effusions/significant edema.

Suggested supportive care:

- Bactrim should be held beginning on day of HD MTX infusion, and not re-started until MTX level is non-detectable detectable or <0.1 micromolar (as per institutional standard).
- Nonsteroidal anti-inflammatory medications should also be held beginning on day of HD MTX infusion, and not re-started until MTX level is non-detectable or <0.1 micromolar (as per institutional standard).

See Section for Dose Modifications. See Section for allowable deviations in timing of medications/procedures and for allowable variation in dosing.

4.9.3 Consolidation I Phase for Standard Risk Patients

One 3-week cycle of therapy, administered as follows:

Days	1	8	15	22
	V			
	6MP	-----		
	ITM			
	HDM			

Note: Patients should continue to receive tapering doses of prednisone or methylprednisolone at the same time that they begin Consolidation I Phase.

4.9.4 Dosages, Schedules & Routes

- | | | |
|-----|---------------------------|--|
| V | Vincristine | 2 mg/m ² (maximum dose 2 mg) IV push or IV via minibag on Day 1 |
| 6MP | 6-mercaptopurine | 50 mg/m ² /day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount. |
| ITM | Intrathecal Methotrexate. | Administer on Day 1 (prior to starting methotrexate infusion, if possible) (Note: Induction Day 32 ITM can be considered to be Day 1 Consolidation I ITM if given within 72 hours of beginning Consolidation I systemic chemotherapy). |

Dose according to age:

Age	1 - 1.99yrs	2 - 2.99 yrs	≥ 3 yrs
Methotrexate	8mg	10 mg	12 mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

HDM High dose methotrexate. Begin infusion on Day 1

- Prehydrate with IVF containing NaHCO₃ until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0 . Suggested prehydration: D5W + 75 mEq NaHCO₃/L at 125 mL/m²/hour for 6 hours
- Hour 0: Total fluid while receiving methotrexate infusion: patient should receive total fluids of at least 125 mL/m²/hour with NaHCO₃-containing fluids beginning at Hour 0 and continuing until methotrexate level non-detectable or <0.1 micromolar (as per institutional standard). Fluid volume may be adjusted to maintain dilute urine (sg ≤ 1.010) until methotrexate non-detectable (or <0.1 micromolar). Fluid should contain NaHCO₃, and amount of NaHCO₃ should be adjusted to maintain urine pH ≥ 7 and ≤ 8 . Suggested starting concurrent IVF: D5W + 75 mEq NaHCO₃/L at 125 mL/m²/hour
- Hour 0: Methotrexate 0.5 grams/m² IV over 30 minutes. Suggested diluent: 10 mL D5W + 75 mEq NaHCO₃/L to run at 20 mL/hour (along with concurrent IVF).
- Hour 0.5-24: Methotrexate 4.5 grams/m² continuous infusion IV over 23.5 hours. Suggested diluent: 470 mL D5W + 75 mEq NaHCO₃/L to run at 20 mL/hour for 23.5 hours (along with concurrent IVF).
- Hour 24: Check MTX level. (**Note: check level at completion of infusion**)
- Hour 36: Leucovorin 75 mg/m² IV bolus x 1 dose, given 36 hours after start of MTX infusion
- Hour 42: Leucovorin 15 mg/m² IV bolus every 6 hours until methotrexate level is non-detectable or <0.1 micromolar (as per institutional standard). Once MTX level is non-detectable (or <0.1 micromolar), discontinue leucovorin and IV hydration/alkalinization.
- Hour 48: Check methotrexate level. Continue to check at least every 24 hours until methotrexate level non-detectable or <0.1 micromolar, as per institutional standard.

Dose adjustments for high methotrexate levels

- Hour 24: If level > 100 micromolar, increase total fluids to at least 200 mL/m²/hour and start leucovorin 100 mg/m²/dose IV bolus every 3 hours. Check MTX level every 12 hours, if possible. Continue at this dose of leucovorin until level is < 5 micromolar, then reduce dose of leucovorin to 15 mg/m² IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).
- Hour 48: If level > 0.18 but < 5 micromolar, increase total fluids to at least 200 mL/m²/hour and continue leucovorin at 15 mg/m² IV every 6 hours. If level > 5 micromolar, increase total fluids to at least 200 mL/m²/hour and change leucovorin

- dosing to 15 mg/m²/dose IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).
- Hour 72: If level > 0.1 but < 5 micromolar, ensure total fluids are at least 200 mL/m²/hour and continue leucovorin at 15 mg/m²/dose IV every 6 hours. If level > 5 micromolar, ensure total fluids are at least 200 mL/m²/hour and change leucovorin dosing to 15 mg/m²/dose IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).
- Note: Dosing guidelines for fluids and leucovorin (above) may be modified depending on patient's clinical status (such as rising creatinine, new effusions, etc). In rare circumstances, methotrexate infusion may be stopped early in the event of excessive toxicity (such as rising creatinine). Any modifications should be discussed in advance with Lewis Silverman, MD, or designee.

4.10 **CONSOLIDATION I PHASE: HIGH RISK PATIENTS**

4.10.1 **Starting Time:** Patients must be in documented remission at all sites.

4.10.2 **Starting Criteria:** APC $\geq$ 1,000, platelets $\geq$ 100,000, direct bilirubin $\leq$ 1.4 mg/dL (23.9 micromoles/L), SGOT $\leq$ 8 x normal, creatinine normal for age, no mucositis, no ascites/effusions/significant edema.

Suggested supportive care:

- Bactrim should be held beginning on day of HD MTX infusion, and not re-started until MTX level is non-detectable or <0.1 micromolar (as per institutional standard).
- Nonsteroidal anti-inflammatory medications should also be held beginning on day of HD MTX infusion, and not re-started until MTX level is non-detectable or <0.1 micromolar (as per institutional standard).
- MTX infusion should be started at least 8 hours and not more than 24 hours following the dose of doxorubicin.

See Section for Dose Modifications. See Section for allowable deviations in timing of medications/procedures and for allowable variation in dosing.

4.10.3 **Consolidation I Phase for High Risk Patients**

One 3-week cycle of therapy, administered as follows:

Cycle 1

Days	1	8	15	22
	V			
	6MP	-----		
	Dd			
	ITM			
	HDM			

Note: Patients should continue to receive tapering doses of prednisone or methylprednisolone at the same time that they begin Consolidation I Phase.

4.10.4 **Dosages, Schedules & Routes**

- | | | |
|-----|------------------|--|
| V | Vincristine | 2 mg/m ² (maximum dose 2 mg) IV push or IV via minibag on Day 1 |
| 6MP | 6-mercaptopurine | 50 mg/m ² /day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount. |

- Dd Doxorubicin 30 mg/m² IV preceded by dexrazoxane 300 mg/m² IV on Day 1.
Suggested administration for both drugs:
- Minute 0 Dexrazoxane over 15 minutes
 - Minute 15 Doxorubicin IV push via central line or freshly placed peripheral IV
 - Goal is no more than 30 minutes maximum elapsed administration time combined for both drugs
 - May give doxorubicin prior to dexrazoxane if given via peripheral IV
 - May give doxorubicin IV over 15 minutes if given via central line

ITM Intrathecal Methotrexate. Administer on Day 1 (prior to starting methotrexate infusion, if possible). (**Note:** Induction Day 32 ITM can be considered to be Day 1 Consolidation I ITM if given within 72 hours of beginning Consolidation I systemic chemotherapy).

Dose according to age:

Age	1 - 1.99yrs	2 - 2.99 yrs	≥ 3 yrs
Methotrexate	8mg	10 mg	12 mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

HDM High dose methotrexate. **Begin infusion at least 8 hours but no more than 24 hours following the dose of doxorubicin**

- Prehydrate with IVF containing NaHCO₃ until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Suggested prehydration: D5W + 75 mEq NaHCO₃/L at 125 mL/m²/hour for 6 hours
- Hour 0: Total fluid while receiving methotrexate infusion: patient should receive total fluids of at least 125 mL/m²/hour with NaHCO₃-containing fluids beginning at Hour 0 and continuing until methotrexate level non-detectable or <0.1 micromolar (as per institutional standard). Fluid volume may be adjusted to maintain dilute urine (sg ≤ 1.010) until methotrexate non-detectable (or <0.1 micromolar). Fluid should contain NaHCO₃, and amount of NaHCO₃ should be adjusted to maintain urine pH ≥ 7 and ≤ 8. Suggested starting concurrent IVF: D5W + 75 mEq NaHCO₃/L at 125 mL/m²/hour
- Hour 0: Methotrexate 0.5 grams/m² IV over 30 minutes. Suggested diluent: 10 mL D5W + 75 mEq NaHCO₃/L to run at 20 mL/hour (along with concurrent IVF).
- Hour 0.5-24: Methotrexate 4.5 grams/m² continuous infusion IV over 23.5 hours. Suggested diluent: 470 mL D5W + 75 mEq NaHCO₃/L to run at 20 mL/hour for 23.5 hours (along with concurrent IVF).
- Hour 24: Check MTX level. (**Note: check level at completion of infusion**)
- Hour 36: Leucovorin 75 mg/m² IV bolus x 1 dose, given 36 hours after start of MTX infusion

- Hour 42: Leucovorin 15 mg/m² IV bolus every 6 hours until methotrexate level is non-detectable or <0.1 micromolar (as per institutional standard). Once MTX level is non-detectable (or <0.1 micromolar), discontinue leucovorin and IV hydration/alkalinization.
- Hour 48: Check methotrexate level. Continue to check every 24 hours until methotrexate level non-detectable or <0.1 micromolar, as per institutional standard.

Dose adjustments for high methotrexate levels

- Hour 24: If level > 100 micromolar, increase total fluids to at least 200 mL/m²/hour and start leucovorin 100 mg/m²/dose IV bolus every 3 hours. Check MTX level every 12 hours if possible. Continue at this dose of leucovorin until level is < 5 micromolar, then reduce dose of leucovorin to 15 mg/m² IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).
- Hour 48: If level > 0.18 but < 5 micromolar, increase total fluids to at least 200 mL/m²/hour and continue leucovorin at 15 mg/m² IV every 6 hours. If level > 5 micromolar, increase total fluids to at least 200 mL/m²/hour and change leucovorin dosing to 15 mg/m²/dose IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).
- Hour 72: If level > 0.1 but < 5 micromolar, ensure total fluids are at least 200 mL/m²/hour and continue leucovorin at 15 mg/m²/dose IV every 6 hours. If level > 5 micromolar, ensure total fluids are at least 200 mL/m²/hour and change leucovorin dosing to 15 mg/m²/dose IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).

Note: Dosing guidelines for fluids and leucovorin (above) may be modified depending on patient's clinical status (such as rising creatinine, new effusions, etc). In rare circumstances, methotrexate infusion may be stopped early in the event of excessive toxicity (such as rising creatinine). Any modifications should be discussed in advance with Lewis Silverman, MD, or designee.

4.11 **CONSOLIDATION I: VERY HIGH RISK PATIENTS**

Consolidation I Therapy for Very High Risk Patients consists of 3 phases

- Consolidation IA: vincristine, 6MP, doxorubicin/dexrazoxane, high dose methotrexate, ITM
- Consolidation IB: cyclophosphamide, low-dose cytarabine, 6MP, ITM
- Consolidation IC: high-dose cytarabine, etoposide, dexamethasone, asparaginase

4.11.1 Starting Time: Patients must be in documented remission at all sites.

4.11.2 Starting Criteria (Cycle IA): $APC \geq 1,000$, platelets $\geq 100,000$, direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L), SGOT ≤ 8 x normal, creatinine normal for age, no mucositis, no ascites/effusions/significant edema.

Suggested supportive care:

- Bactrim should be held beginning on day of HD MTX infusion, and not re-started until MTX level is non-detectable or <0.1 micromolar (as per institutional standard).
- Nonsteroidal anti-inflammatory medications should also be held beginning on day of HD MTX infusion, and not re-started until MTX level is non-detectable or <0.1 micromolar (as per institutional standard).
- MTX infusion should be started at least 8 hours and not more than 24 hours following the dose of doxorubicin.

See Section for Dose Modifications. See Section for allowable deviations in timing of medications/procedures and for allowable variation in dosing.

4.11.3 **Consolidation IA (VHR patients):**

Days	1	15	22
	V		
	6MP-----		
	Dd		
	ITM		
	HDM		

Note: Patients should continue to receive tapering doses of prednisone or methylprednisolone at the same time that they begin Consolidation I Phase.

4.11.4 **Dosages, Schedules & Routes**

V	Vincristine	2 mg/m ² (maximum dose 2 mg) IV push or IV via minibag on Day 1
6MP	6-mercaptopurine	50 mg/m ² /day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount.

- Dd Doxorubicin 30 mg/m² IV preceded by dexrazoxane 300 mg/m² IV on Day 1.
Suggested administration for both drugs:
- Minute 0 Dexrazoxane over 15 minutes
 - Minute 15 Doxorubicin IV push via central line or freshly placed peripheral IV
 - Goal no more than 30 minutes maximum elapsed administration time combined for both drugs
 - May give doxorubicin prior to dexrazoxane if given via peripheral IV
 - May give doxorubicin IV over 15 minutes if given via central line

ITM Intrathecal Methotrexate. Administer on Day 1, prior to starting methotrexate infusion if possible. (**Note:** Induction Day 32 ITM can be considered to be Day 1 Consolidation I ITM if given within 72 hours of beginning Consolidation IA systemic chemotherapy).
Dose according to age:

Age	1 - 1.99yrs	2 - 2.99 yrs	≥ 3 yrs
Methotrexate	8 mg	10 mg	12 mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

HDM High dose methotrexate. **Begin infusion at least 8 hours but no more than 24 hours following the dose of doxorubicin**

- Prehydrate with IVF containing NaHCO₃ until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Suggested prehydration: D5W + 75 mEq NaHCO₃/L at 125 mL/m²/hour for 6 hours
- Hour 0: Total fluid while receiving methotrexate infusion: patient should receive total fluids of at least 125 mL/m²/hour with NaHCO₃-containing fluids beginning at Hour 0 and continuing until methotrexate level non-detectable or <0.1 micromolar (as per institutional standard). Fluid volume may be adjusted to maintain dilute urine (sg ≤ 1.010) until methotrexate non-detectable (or <0.1 micromolar). Fluid should contain NaHCO₃, and amount of NaHCO₃ should be adjusted to maintain urine pH ≥ 7 and ≤ 8. Suggested starting concurrent IVF: D5W + 75 mEq NaHCO₃/L at 125 mL/m²/hour
 - Hour 0: Methotrexate 0.5 grams/m² IV over 30 minutes. Suggested diluent: 10 mL D5W + 75 mEq NaHCO₃/L to run at 20 mL/hour (along with concurrent IVF).
 - Hour 0.5-24: Methotrexate 4.5 grams/m² continuous infusion IV over 23.5 hours. Suggested diluent: 470 mL D5W + 75 mEq NaHCO₃/L to run at 20 mL/hour for 23.5 hours (along with concurrent IVF).
 - Hour 24: Check MTX level (**Note: check level at completion of infusion**).

- Hour 36: Leucovorin 75 mg/m² IV bolus x 1 dose, given 36 hours after start of MTX infusion
- Hour 42: Leucovorin 15 mg/m² IV bolus every 6 hours until methotrexate level is non-detectable. Once MTX level is non-detectable (or <0.1 micromolar), discontinue leucovorin and IV hydration/alkalinization or <0.1 micromolar (as per institutional standard).
- Hour 48: Check methotrexate level. Continue to check every 24 hours until methotrexate level non-detectable or <0.1 micromolar, as per institutional standard.

Dose adjustments for high methotrexate levels

- Hour 24: If level > 100 micromolar, increase total fluids to at least 200 mL/m²/hour and start leucovorin 100 mg/m²/dose IV bolus every 3 hours. Check MTX level every 12 hours. Continue at this dose of leucovorin until level is < 5 micromolar, then reduce dose of leucovorin to 15 mg/m² IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).
- Hour 48: If level > 0.18 but < 5 micromolar, increase total fluids to at least 200 mL/m²/hour and continue leucovorin at 15 mg/m² IV every 6 hours. If level > 5 micromolar, increase total fluids to at least 200 mL/m²/hour and change leucovorin dosing to 15 mg/m²/dose IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).
- Hour 72: If level > 0.1 but < 5 micromolar, ensure total fluids are at least 200 mL/m²/hour and continue leucovorin at 15 mg/m²/dose IV every 6 hours. If level > 5 micromolar, ensure total fluids are at least 200 mL/m²/hour and change leucovorin dosing to 15 mg/m²/dose IV every 3 hours. Continue this dose of leucovorin until level is non-detectable or <0.1 micromolar (as per institutional standard).

Note: Dosing guidelines for fluids and leucovorin (above) may be modified depending on patient's clinical status (such as rising creatinine, new effusions, etc). In rare circumstances, methotrexate infusion may be stopped early in the event of excessive toxicity (such as rising creatinine). Any modifications should be discussed in advance with Lewis Silverman, MD, or designee.

4.11.5 Consolidation IB (VHR patients)

The second phase of VHR Consolidation I (Consolidation IB) may start approximately 21 days after the start of Consolidation IA, and only when there is no or nearly fully resolved mucositis and when $APC \geq 750$, and platelets $\geq 75,000$ and rising. Other starting criteria for starting Consolidation IB: creatinine normal for age, $SGOT \leq 8 \times$ normal, direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L).

Peripheral blood for MRD should be drawn prior to starting cycle.

Days	1	2...	9...	15
Cyc				
		Ara	Ara	
		6MP-----		
		ITM		

4.11.6 Dosages, Schedules & Routes

Cyc Cyclophosphamide 1000 mg/m² IV over 1 hour on Day 1

Suggested administration:

- Prehydration: NS 20 mL/kg IV over 1 hour, then D5 ½ NS at 125 mL/m²/hour until urine s.g. < 1.010
- **Optional: Prior to hour 0** - Mesna 360 mg/m² IV over 15 minutes in concurrent IVF just prior to Cyclophosphamide.
- Hour 0: Cyclophosphamide 1000 mg/m² IV in 125 mL/m² D5 ½ NS over 1 hour
- Posthydration (Begin Hour 1): D5 ½ NS at 125 mL/m²/hour x 4 hours
- **Optional:** Hour 3: Mesna 360 mg/m² IV over 15 minutes in concurrent IVF

Note: Use of Mesna is not required, and its administration is at the discretion of treating physician. Duration of pre- and post-hydration is also at the discretion of treating physician.

Ara Cytarabine (ara-C) 75 mg/m²/day IV push on Days 2-5 and 9-12.

6MP 6-mercaptopurine 50 mg/m²/day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount.

ITM IT methotrexate. Administer on Day 1.

Dose according to age:

Age	1 - 1.99yrs	2 - 2.99yrs	$\geq$ 3yrs
Methotrexate	8mg	10mg	12mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
 - Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.
-

4.11.7 Consolidation IC (VHR patients)

The third phase of VHR Consolidation I (Consolidation IC) should start approximately 21 days after the start of Consolidation IB, and only when there is no or nearly fully resolved mucositis and when $APC \geq 750$ and platelets $\geq 75,000$, and rising.

Criteria to administer Day 8 Asparaginase: Direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L). Suggestion: check amylase prior to administration of asparaginase.

Peripheral blood for MRD should be drawn prior to starting cycle.

Days	1	2	3	4	5...	8
	HDara	HDara				
			Etop	Etop	Etop	
	Dex-----					ASP

4.11.8 Dosages, Schedules & Routes

HDara High-dose Cytarabine (ara-C) 2 grams/m²/dose IV every 12 hours for a total of four doses beginning on Day 1. Suggested Administration Guidelines: Give each dose of cytarabine in 300 mL/m² D5 ¼ NS over 3 hours at 100 mL/m²/hour

Suggested Supportive Care: Dexamethasone ophthalmic ointment/drops: apply to both eyes every 6 hours beginning with 1st dose of Cytarabine and continue until 48 hours after completion of Cytarabine.

Etop Etoposide (VP16) 100 mg/m²/dose IV daily on Days 3, 4, and 5 (three doses total). Suggested Administration Guidelines: Give each dose in 250 mL/m² D5 1/2 NS over 1 hour.

Dex Dexamethasone 18 mg/m²/day orally or IV divided twice daily (bid) on Days 1-5 (ten total doses)

ASP Asparaginase according to randomization, beginning on Day 8. Mix in 100 mL Normal Saline and give over 1 hour.

- A. SC-PEG Asparaginase (Calaspargase Pegol) 2500 IU/m²/dose IV every 3 weeks,
- or
- B. Oncaspar 2500 IU/m²/dose IV every 2 weeks.

Note: Asparaginase should continue through CNS phase and Consolidation II phase for 30 total weeks (10 total post-induction doses of SC-PEG given every 3-weeks or 15 total post-induction doses of Oncaspar given every 2-weeks).

Note: All patients should have asparaginase enzyme (PK) samples obtained immediately prior to first dose of asparaginase and then prior to every subsequent dose of asparaginase.

4.12 **CNS PHASE FOR STANDARD RISK PATIENTS**

4.12.1 Starting time: 21 days from start of Consolidation I, as soon as starting criteria are met. See Section for allowable deviations in timing.

4.12.2 Starting Criteria: $APC \geq 1,000$, platelets $\geq 100,000$, direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L), SGOT ≤ 8 x normal, no or nearly fully resolved mucositis. Suggestion: check amylase prior to administration of asparaginase).

Note: Asparaginase should only be administered on Day 1 for SR patients if all criteria for starting CNS phase are met.

See Section for Dose Modifications. See Section for allowable deviations in timing of medications/procedures and for allowable variation in dosing.

4.12.3 Dosages, Schedules & Routes

- Vincristine 2 mg/m^2 (maximum dose 2 mg) IV push or IV via minibag x 1 dose on Day 1.
- 6-mercaptopurine $50 \text{ mg/m}^2/\text{day}$ orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount.
- Dexamethasone $6 \text{ mg/m}^2/\text{day}$ orally divided twice daily (bid) for 5 days beginning on Day 1.
- Asparaginase according to randomization on Day 1. Mix in 100 mL Normal Saline and give over 1 hour.
 - A. SC-PEG Asparaginase (Calaspargase Pegol) $2500 \text{ IU/m}^2/\text{dose}$ IV every 3 weeks,
 - or
 - B. Oncaspar $2500 \text{ IU/m}^2/\text{dose}$ IV every 2 weeks.

Note: Asparaginase should continue through CNS phase and Consolidation II phase for 30 total weeks (10 total post-induction doses of SC-PEG given every 3-weeks or 15 total post-induction doses of Oncaspar given every 2-weeks). Direct bilirubin should be ≤ 1.4 mg/dL (23.9 micromoles/L) for all doses of asparaginase, including 2nd dose of asparaginase in the CNS phase.

Note: All patients should have asparaginase enzyme (PK) samples obtained immediately prior to first dose of asparaginase and then prior to every subsequent dose of asparaginase.

- Intrathecal Methotrexate/Cytarabine/Hydrocortisone twice weekly x 4 doses

Age	1 - 1.99 yrs	2 - 2.99yrs	≥ 3yrs
Methotrexate	8mg	10mg	12mg
Cytarabine	20mg	30mg	40mg
Hydrocortisone	9mg	12mg	15mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

4.13 **CNS PHASE: HIGH RISK AND VERY HIGH RISK PATIENTS**

4.13.1 Starting time: 21 days from start of Consolidation I, as soon as starting criteria are met. For VHR patients, starting time is 21 days from start of **Consolidation IC**. See Section for allowable deviations in timing.

4.13.2 Starting Criteria: $APC \geq 1,000$, platelets $\geq 100,000$, direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L), SGOT ≤ 8 x normal, no or nearly fully resolved mucositis. Suggestion: check amylase prior to administration of asparaginase.

Note: Asparaginase should only be administered on Day 1 for HR patients if all criteria for starting CNS phase are met.

For VHR leukemia patients and T-ALL patients: Bone marrow aspirate for MRD assessment should be performed at the same time as first lumbar puncture of CNS phase and blood for MRD should be drawn prior to starting cycle.

See Section for Dose Modifications. See Section for allowable deviations in timing of medications/procedures and for allowable variation in dosing.

4.13.3 Dosages, Schedules & Routes

- Vincristine 2 mg/m² (maximum dose 2 mg) IV push or IV via minibag x 1 dose on Day 1.
- Doxorubicin 30 mg/m² IV bolus and Dexrazoxane 300 mg/m² IV bolus. Give on Day 1.

Suggested administration for both drugs:

- Minute 0 Dexrazoxane over 15 minutes
- Minute 15 Doxorubicin IV push via central line or freshly placed peripheral IV
- Goal no more than 30 minutes maximum elapsed administration time combined for both drugs
- May give doxorubicin prior to dexrazoxane if given via peripheral IV
- May give doxorubicin IV over 15 minutes if given via central line
- 6-mercaptopurine 50 mg/m²/day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount.
- Dexamethasone 18 mg/m²/day orally divided twice daily (bid) for 5 days beginning on Day 1.
- Asparaginase according to randomization on Day 1. Mix in 100 mL Normal Saline and give over 1 hour.
 - A. SC-PEG Asparaginase (Calaspargase Pegol) 2500 IU/m²/dose IV every 3 weeks,
or
 - B. Oncaspar 2500 IU/m²/dose IV every 2 weeks.

Note: Asparaginase should continue through CNS phase and Consolidation II phase for 30 total weeks (10 total post-induction doses of SC-PEG given every 3-weeks or 15 total post-induction doses of Oncaspar given every 2-weeks). Direct bilirubin should be ≤ 1.4 mg/dL (23.9 micromoles/L) for all doses of asparaginase, including 2nd dose of asparaginase in the CNS phase.Note: VHR patients who began asparaginase during the Consolidation IC phase should continue to receive asparaginase per randomization at the frequency indicated in; that is, during the CNS phase, asparaginase should only be administered 21 days after the previous dose of SC-PEG Asparaginase or 14 days after the previous dose of Oncaspar (and not necessarily on Day 1 of CNS phase).

Note: All patients should have asparaginase enzyme (PK) samples obtained immediately prior to first dose of asparaginase and then prior to every subsequent dose of asparaginase.

- Intrathecal Methotrexate/Cytarabine/Hydrocortisone twice weekly x 4 doses

Age	1 - 1.99 yrs	2 - 2.99 yrs	≥ 3 yrs
Methotrexate	8 mg	10 mg	12 mg
Cytarabine	20 mg	30 mg	40 mg
Hydrocortisone	9 mg	12 mg	15 mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.

4.13.4 **Cranial Radiation:**

To be administered only to:

- VHR patients and
- HR B-precursor ALL patients with any of the following criteria:
 - CNS-3 at diagnosis or at Day 18 (or any time after Day 18 but prior to Day 32)
 - CNS-2 at Day 18 or at end of remission induction
- T-ALL (all patients, regardless of CNS status)
- Lymphoblastic lymphoma patients (regardless of phenotype) who meet any of the following criteria:
 - CNS-3 at diagnosis or at Day 18 (or any time after Day 18 but prior to Day 32)
 - CNS-2 at Day 18 or at end of remission induction

- Dosage of Cranial Radiation: 1200 cGy cranial radiation delivered as 150 cGy daily fractions for 8 days. NOTE: Cranial radiation should start as close as possible to the administration of doxorubicin/vincristine.
- Exception: Dosage of 1800 cGy (180 cGy fractions for 10 days) should be administered to patients with the following characteristics:
 - CNS-3 at diagnosis or at Day 18
 - CNS-2 at Day 18 or at end of remission induction

See Table 6.13 (below) for summary of radiation dose for high risk/very high risk patients based on presenting characteristics, CNS status

4.14 CONSOLIDATION II PHASE

4.14.1 Starting Time for All Patients

Starting time: after recovery from CNS Therapy (21 days from start of systemic chemotherapy administered during CNS Therapy and as soon as starting criteria are met). See Section for allowable deviations in starting time.

4.14.2 Criteria to begin Consolidation II Cycles

APC = (Total WBC) x %(Monos + Polys + Bands)

- To begin 1st week of each 3-week chemotherapy cycle:
 - $APC \geq 750/\text{mm}^3$
 - Platelets $\geq 75,000/\text{mm}^3$
 - Mucositis: none or mild
 - $SGOT \leq 8 \times \text{normal}$
 - Direct bilirubin $\leq 1.4 \text{ mg/dl}$ (23.9 micromoles/L)
- If criteria are not met, hold chemo for 1-7 days, and then re-check.
- In unusual circumstances, chemotherapy cycles may be started even when not all of these criteria have been met if approved in advance by Principal Investigator or designee.
- Note: These criteria do not apply to scheduled doses of asparaginase.

4.14.3 Criteria to continue cycle (Days 2 - 21):

- $APC \geq 500/\text{mm}^3$
- Platelets $\geq 50,000/\text{mm}^3$
- Mucositis: none or mild
- $SGOT \leq 8 \times \text{normal}$
- Direct bilirubin $\leq 1.4 \text{ mg/dl}$ (23.9 micromoles/L)
- Note: These criteria do not apply to scheduled doses of asparaginase

4.14.4 Criteria to administer asparaginase

- No clinical pancreatitis
- No new, untreated deep venous thrombosis
- Direct bilirubin ≤ 1.4 mg/dL (23.9 micromoles/L)
- Note: Asparaginase should be administered regardless of blood counts, mucositis, or SGOT.

See Section for Dose Modifications. See Section for allowable deviations in timing of medications/procedures and for allowable variation in dosing.

4.14.5 **CONSOLIDATION II THERAPY FOR STANDARD RISK PATIENTS**

Week	1*	2	3	4	5	6
	V			V		
	Dex			Dex		
	6MP	6MP		6MP	6MP	
	m	m	m	m	m	m
Arm A ASP	SC-PEG			SC-PEG		
Arm B ASP	Oncaspar		Oncaspar		Oncaspar	

Continue Asparaginase (according to randomization) for 30 weeks (10 post-induction doses of SC-PEG or 15 post-induction doses of Oncaspar). Proceed to Continuation Therapy after 30 post-remission weeks of asparaginase have been administered.

*** IT MAH - to be given every 9 weeks x 6 doses. First lumbar puncture with IT MAH during Consolidation II is 9 weeks after start of CNS treatment. After 6 doses of IT MAH (given every 9 weeks) completed, change to IT MAH every 18 weeks until end of therapy. IT medications should only be given at the start of a chemotherapy cycle.**

All outpatient chemotherapy for each cycle must be prescribed by a physician, nurse practitioner or physician assistant, as per institutional standard, on the day that the patient is evaluated and found to meet criteria for that cycle. This means that only one cycle of outpatient chemotherapy may be prescribed at each visit, and refills for chemotherapy prescriptions are not allowed for study patients. Exception can be made for patients receiving Purixan® (6-MP oral suspension) who must be dispensed full bottles per medical insurance restrictions; in these cases, medical staff should review dosing with patient/family at the start of each cycle. Under no circumstances may other clinical staff call in prescriptions for chemotherapy for patients on study.

See Section for Dose Modifications.

Dosages, Schedules & Routes

V	Vincristine	2 mg/m ² (maximum dose 2 mg) IV push or IV via minibag on Day 1 of cycle
Dex	Dexamethasone	6 mg/m ² /day orally divided twice daily (bid) for 5 days on beginning on Day 1 of cycle
6MP	6-mercaptopurine	50 mg/m ² /day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount.

m Methotrexate 30 mg/m² IV push or IM once a week (Days 1, 8 and 15 of each cycle). Hold systemic methotrexate on the week IT Methotrexate is given.

ASP Asparaginase according to randomization. Mix in 100 mL Normal Saline and give over 1 hour.

- A. SC-PEG Asparaginase (Calaspargase Pegol) 2500 IU/m²/dose IV every 3 weeks,
or
 B. Oncaspar 2500 IU/m²/dose IV every 2 weeks.

Note: Administer asparaginase only if direct bilirubin $\leq$ 1.4 mg/dL (23.9 micromoles/L). Asparaginae may be administered regardless of blood counts.

Note: Asparaginase should continue through Consolidation II phase for 30 total weeks (10 total post-induction doses of SC-PEG given every 3-weeks or 15 total post-induction doses of Oncaspar given every 2-weeks).

Note: All patients should have asparaginase enzyme (PK) samples obtained immediately prior each dose of asparaginase.

IT MAH Intrathecal Methotrexate/Cytarabine/Hydrocortisone

Give as close to every 9 weeks as possible for 6 doses, then give as close to every 18 weeks. Always give IT medications at the start of a chemo cycle. First dose is given 9 weeks after first lumbar puncture administered during CNS treatment.

Age	1 - 1.99yrs	2 - 2.99 yrs	$\geq$ 3 yrs
Methotrexate	8 mg	10 mg	12 mg
Cytarabine	20 mg	30 mg	40 mg
Hydrocortisone	9 mg	12 mg	15 mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.
- Hold systemic methotrexate on the week IT Methotrexate is given

4.14.6 CONSOLIDATION II THERAPY FOR HIGH RISK AND VERY HIGH RISK PATIENTS

Week	1	2	3	4	5	6
	V			V		
	Dex			Dex		
	6MP	6MP		6MP	6MP	
	Dd			D(d)		
	(m)**					
Arm A ASP	SC-PEG			SC-PEG		
Arm B ASP	Oncaspar		Oncaspar		Oncaspar	

Continue Asparaginase (according to randomization) for 30 weeks (10 post-induction doses of SC-PEG or 15 post-induction doses of Oncaspar).

- **Repeat this 3 week sequence of treatment until ready for next phase of therapy. Proceed to Continuation Therapy after all of the following have been administered:**
 - **Cumulative doxorubicin dosage of 300 mg/m² +/- 15 mg/m²**
 - **30 post-remission weeks of asparaginase**
 - **10 cycles with high-dose dexamethasone (18 mg/m²/day), including dexamethasone administered during the CNS phase (but, for VHR patients, not including dexamethasone administered during Consolidation IC phase).**

IT MAH – frequency of administration depends on whether or not patient received cranial radiation. If no cranial radiation, first IT dose is given 9 weeks after first lumbar puncture during CNS Therapy. If patient received cranial radiation, first IT dose is given 18 weeks after first lumbar puncture during CNS Therapy. IT medications should only be given at the start of a chemotherapy cycle.

All outpatient chemotherapy for each cycle must be prescribed by a physician, nurse practitioner or physician assistant, as per institutional standard, on the day that the patient is evaluated and found to meet criteria for that cycle. This means that only one cycle of outpatient chemotherapy may be prescribed at each visit, and refills for chemotherapy prescriptions are not allowed for study patients. Exception can be made for patients receiving Purixan® (6-MP oral suspension) who must be dispensed full bottles per medical insurance restrictions; in these cases, medical staff should review dosing with patient/family at the start of each cycle. Under no circumstances may other clinical staff call in prescriptions for chemotherapy for patients on study.

See Section for Dose Modifications.

Dosages, Schedules & Routes

V Vincristine 2 mg/m² (maximum dose 2 mg) IV push or IV via minibag on Day 1 of cycle

Dex Dexamethasone 18 mg/m²/day orally divided twice daily (bid) for 5 days beginning on Day 1 of cycle.

Note: Patients should receive a total of 10 cycles with high-dose dexamethasone (18 mg/m²/day), including the CNS phase (but not including the Consolidation IC phase for VHR patients). After 10 cycles have been administered at this dose, the dose of dexamethasone for all subsequent cycles should be 6 mg/m²/day orally divided twice daily (bid) for 5 days beginning on Day 1 of chemotherapy cycle, even if patient is still receiving Asparaginase and/or Doxorubicin.

6MP 6-mercaptopurine 50 mg/m²/day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount.

Dd Doxorubicin 30 mg/m² IV preceded by Dexrazoxane 300 mg/m² IV on Day 1 of cycle.

Suggested administration for both drugs:

- Minute 0 Dexrazoxane over 15 minutes
- Minute 15 Doxorubicin IV push via central line or freshly placed peripheral IV
- Goal: no more than 30 minutes maximum elapsed administration time combined for both drugs
- May give doxorubicin prior to dexrazoxane if given via peripheral IV
- May give doxorubicin IV over 15 minutes if given via central line

****Stop doxorubicin when total cumulative dose is 300 mg/m² ± 15mg/m² (cumulative dose of 300 mg/m²+ 15 mg/m² is to allow for variability in cumulative drug dosing; for those patients receiving 24 mg/m² as a result of dose reduction it is not possible to receive exactly 300 mg/m²). After achieving cumulative dose of 300 mg/m² ± 15 mg/m² of doxorubicin, begin weekly methotrexate at the start of the next cycle as indicated below.**

When doxorubicin completed and weekly methotrexate started, give as follows:

m Methotrexate 30 mg/m² IV push or IM once a week, beginning on Day 1 of a cycle. Maximum dose for previously irradiated patients is 40 mg/m². Hold systemic methotrexate on the week IT Methotrexate is given.

ASP Asparaginase according to randomization. Mix in 100 mL Normal Saline and give over 1 hour.

- A. SC-PEG Asparaginase (Calaspargase Pegol) 2500 IU/m²/dose IV every 3 weeks,
or
 B. Oncaspar 2500 IU/m²/dose IV every 2 weeks.

Note: Administer asparaginase only if direct bilirubin $\leq$ 1.4 mg/dL (23.9 micromoles/L) . Asparaginae may be administered regardless of blood counts.

Note: Asparaginase should continue through Consolidation II phase for 30 total weeks (10 total post-induction doses of SC-PEG given every 3-weeks or 15 total post-induction doses of Oncaspar given every 2-weeks).

Note: All patients should have asparaginase enzyme (PK) samples obtained immediately prior each dose of asparaginase.

IT MAH Intrathecal Methotrexate/Cytarabine/Hydrocortisone

No prior cranial radiation: Give as close to every 9 weeks as possible for 6 doses, then give as close to every 18 weeks. Always give IT medications at the start of a chemo cycle. First dose is given 9 weeks after first lumbar puncture administered during CNS treatment.

Prior cranial radiation: Give as close to every 18 weeks as possible - at the start of a chemo cycle. First dose is given 18 weeks after first lumbar puncture administered during CNS treatment.

Age	1 - 1.99 yrs	2 - 2.99 yrs	$\geq$ 3 yrs
Methotrexate	8 mg	10 mg	12 mg
Cytarabine	20 mg	30 mg	40 mg
Hydrocortisone	9 mg	12 mg	15 mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration
- Hold systemic methotrexate on the week IT Methotrexate is given

4.15 **CONTINUATION PHASE (for Standard, High Risk and Very High Risk Patients)**

4.15.1 Starting Time: Completion of all components of Consolidation II Phase

For SR: Completion of all post-induction doses of asparaginase

For HR/VHR: Completion of all post-induction doses of asparaginase, administration of 10 cycles high-dose dexamethasone (during CNS and Consolidation II phase), and administration of total cumulative dose of doxorubicin of $300 \text{ mg/m}^2 \pm 15 \text{ mg/m}^2$

4.15.2 Starting Criteria for Chemotherapy for All Patients

$$\text{APC} = (\text{Total WBC}) \times \%(\text{Monos} + \text{Polys} + \text{Bands})$$

- To begin 1st week of each 3-week chemotherapy cycle:
 - $\text{APC} \geq 750/\text{mm}^3$
 - $\text{Platelets} \geq 75,000/\text{mm}^3$
 - Mucositis: none or mild
 - $\text{SGOT} \leq 8 \times \text{normal}$
 - $\text{Direct bilirubin} \leq 1.4 \text{ mg/dl}$ (23.9 micromoles/L)
- If criteria are not met, hold chemo for 1-7 days, and then re-check.
- In unusual circumstances, chemotherapy cycles may be started even when not all of these criteria have been met if approved in advance by Principal Investigator or designee.

4.15.3 Criteria to continue cycle (Days 2 - 21):

- $\text{APC} \geq 500/\text{mm}^3$
- $\text{Platelets} \geq 50,000/\text{mm}^3$
- Mucositis: none or mild
- $\text{SGOT} \leq 8 \times \text{normal}$
- $\text{Direct bilirubin} \leq 1.4 \text{ mg/dl}$ (23.9 micromoles/L)

See Section for Dose Modifications.

4.15.4 Continuation Phase Treatment Schema (all patients)

Week	1	2	3
	V		
	Dex		
	6MP	6MP	
	m	m	m

Repeat this 3-week sequence of treatment until 2 years of CCR.

Intrathecal medications at the start of cycles every 9-18 weeks, depending on prior cranial radiation. IT medications should only be given at the start of a chemotherapy cycle.

All outpatient chemotherapy for each cycle must be prescribed by a physician, nurse practitioner or physician assistant, as per institutional standard, on the day that the patient is evaluated and found to meet criteria for that cycle. This means that only one cycle of outpatient chemotherapy may be prescribed at each visit, and refills for chemotherapy prescriptions are not allowed for study patients. Exception can be made for patients receiving Purixan® (6-MP oral suspension) who must be dispensed full bottles per medical insurance restrictions; in these cases, medical staff should review dosing with patient/family at the start of each cycle. Under no circumstances may other clinical staff call in prescriptions for chemotherapy for patients on study.

See Section for Dose Modifications.

4.15.5 Dosages, Schedules & Routes

V	Vincristine	2 mg/m ² (maximum dose 2 mg) IV push or IV via minibag on Day 1 of cycle
Dex	Dexamethasone	6 mg/m ² /day orally divided twice daily (bid) for 5 days beginning on Day 1 of cycle
6MP	6-mercaptopurine	50 mg/m ² /day orally nightly x 14 consecutive days beginning on Day 1. (Suggested administration guidelines: Give on an empty stomach, at least 2 hours after and 1 hour before food and/or milk). Note: If patient taking tablets, daily dose may be adjusted to accommodate available tablet strengths to achieve total 14-day amount.
m	Methotrexate	30 mg/m ² IV push or IM once a week (Days 1, 8 and 15 of each cycle). Maximum dose for previously irradiated patients is 40 mg/m ² . <u>Hold systemic methotrexate on the week IT Methotrexate is given.</u>

IT MAH: Intrathecal Methotrexate/Cytarabine/Hydrocortisone

- **No prior Cranial Radiation:**
Give as close to every 9 weeks as possible for 6 doses (post-CNS therapy), then give as close to every 18 weeks.
- **Previous Cranial Radiation:**
Give as close to every 18 weeks as possible.

Always give IT medications at the start of a chemotherapy cycle

Doses of IT medication:

Age	1 - 1.99 yrs	2 - 2.99 yrs	≥ 3 yrs
Methotrexate	8 mg	10 mg	12 mg
Cytarabine	20 mg	30 mg	40 mg
Hydrocortisone	9 mg	12 mg	15 mg

- Mix in 6 ml preservative-free normal saline (or use institutional guidelines for dilution).
- Intrathecal medications should be filtered prior to or during administration or according to institute policy for safe administration.
- Hold systemic methotrexate on the week IT Methotrexate is given

4.16 Duration of Therapy

Therapy for all patients should be discontinued 104 weeks (+/- 2 weeks) after complete remission has been documented, even if there have been significant delays or dose modifications during treatment. Therapy should not be stopped in the middle of a 3-week continuation cycle. Participants will be considered “off treatment” Day 21 days after the start of the last cycle they receive during the continuation phase of treatment.

Protocol treatment will be discontinued if any of the following occur:

- Failure to achieve remission at the end of the Remission Induction Phase
- Patient found to have Ph+ (BCR/ABL) ALL
- Disease recurrence
- Development of a second malignancy
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition or compliance with protocol therapy render the participant unacceptable for further treatment in the opinion of the treating investigator

4.17 Duration of Follow Up

All participants (including those who stop treatment early) will be followed indefinitely for disease and survival status, except if a participant withdraws from the study and specifically declines such follow-up.

4.18 Criteria for Removal from Study

- Death
- Lost to follow-up
- Withdrawal of consent for any further data submission

5. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the recommendations listed below.

Toxicity assessments will be done using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

5.1 Dose Modifications/Delays and Toxicity Management

5.1.1 Allowable Dosing Variations/Delays (All Phases)

5.1.2 Allowable Dosing Variation

Variations in drug dosages within 10% of calculated doses are acceptable to allow for ease of drug administration (rounding) and minor changes in BSA/weight.

5.1.3 Allowable Deviations in Timing of Therapy

All attempts should be made to administer therapy and perform procedures on days indicated in protocol. Therapy/procedures may be delayed due to toxicity, as indicated in Dose Modification sections. Delays due to intercurrent illnesses are allowed, but therapy should be re-started as soon as possible. Changes in times of therapy/procedures up to +/- 3 days during Induction, Consolidation I, CNS therapy and Consolidation II, and up to +/- 7 days during Continuation, are allowed for scheduling reasons (weekends, holidays, and patient or provider availability). If longer delays are anticipated for reasons other than severe illness or toxicity, contact Principal Investigator or designee for prior approval.

For medications to be given multiple times per day (for example, IV methylprednisolone during the Induction Phase), all attempts should be made to administer medications at the intervals specified in the protocol. Variations of +/- 3 hours from the specified intervals are acceptable to allow some flexibility in medication administration given the complex care needs of many patients.

If doxorubicin is given by peripheral IV, dexrazoxane may be given immediately after rather than prior to doxorubicin. Goal: no more than 30 minutes duration for administration of both doxorubicin and dexrazoxane, regardless of the order in which the medications are given.

High-dose methotrexate infusion is intended to be given over 24 hours. Variation of +/- 1 hour in duration of infusion is allowed to account for variability in pumps and other unavoidable factors. For all other chemotherapy infusions (IV Oncaspar, IV SC-PEG Asparaginase, Cyclophosphamide, Etoposide), variation in protocol-specified infusion duration of +/- 15 minutes is allowed.

5.1.4 Allowable Deviation in Route of Administration

For patients who are unable to receive IV or IM methotrexate during the continuation phase due to travel or other unusual circumstances, a dose of methotrexate may be given orally, but no more than 3 times over the total duration of treatment. If it is necessary to give methotrexate by mouth more than 3 times, the Principal Investigator must be contacted in advance for approval.

For patients unable to tolerate oral dexamethasone during post-induction treatment phases, IV dexamethasone may be used (same dose as oral dosing).

During all phases of therapy, vincristine may be given either by IV push or IV via minibag per institutional standard.

5.1.5 Allowable Deviation for Bilirubin

A total bilirubin of < 1.4 mg/dL (23.9 micromoles/L) is sufficient to meet the bilirubin criteria for enrollment and starting or continuing a cycle during all phases of treatment. For patients receiving Erwinia asparaginase, direct bilirubin may be checked once per week (ie, does not need to be checked prior to each dose).

5.1.6 Allowable Deviations In Therapy Due to Significant Illness

5.1.6.1 Significant Illness at the end of Induction Therapy

In some circumstances when patients have severe life-threatening illness (e.g. disseminated candidiasis) and are not expected to tolerate myelosuppressive chemotherapy for an extended period of time, but are in documented CR at end of remission induction therapy, Consolidation I and CNS therapy may be delayed and patients may proceed with less intensive chemotherapy, such as vincristine or some or all of the agents included in Consolidation II or Continuation cycles. Additional post-induction agents (e.g. steroid, methotrexate, 6MP, doxorubicin with dexrazoxane) may be added in step-wise fashion as tolerated. All such changes must be discussed with and approved by Lewis Silverman, MD or designee. If CNS phase is to be significantly delayed, patients should receive IT medications every 9 weeks (if possible) until patient is able to commence with CNS phase. Patients should receive Consolidation I and CNS therapy as soon as possible.

5.1.6.2 Significant Illness at the end of Consolidation I

In some circumstances when patients have severe life-threatening illness and are not expected to tolerate intensive chemotherapy for an extended period of time, CNS therapy may be delayed and patients may proceed with modified Consolidation II or Continuation cycles, including some or all of the agents typically included in those cycles (including vincristine, dexamethasone, 6MP, methotrexate, and for HR/VHR patients, doxorubicin/dexrazoxane). Agents may be added in subsequent cycles in a step-wise fashion as tolerated. Asparaginase may be given, according to randomization; once started it should be continued for 30 consecutive weeks if tolerated. All such changes must be discussed with and approved by Lewis Silverman, MD or designee.

Patients should receive IT medications every 9 weeks (if possible) until able to commence with CNS phase. Patients should begin CNS phase as soon as possible

5.1.6.3 Significant Illness During Consolidation I for VHR patients

In circumstances when patients have severe illnesses, and are not expected to tolerate intensive chemotherapy for an extended period of time, Cycle IB or IC may be held even if other starting criteria are met. Patients may proceed with modified Consolidation II or Continuation cycles, including some or all of the agents typically included in those cycles (including vincristine, dexamethasone, 6MP, methotrexate, and doxorubicin/dexrazoxane). Agents may be added in subsequent cycles in a step-wise fashion as tolerated. In general, asparaginase should not be given until Consolidation IC is administered, but exceptions can be made on an individual basis after discussion with Principal Investigator. All modifications must be discussed with and approved by Lewis Silverman, MD or designee. Patients should receive IT medications every 9 weeks (if possible) until able to commence with Consolidation IB/IC. All attempts should be made to proceed with Consolidation IB and IC as soon as possible.

5.1.6.4 Significant Illness During Consolidation II/Continuation

In circumstances when patients have severe illnesses, and are not expected to tolerate myelosuppressive chemotherapy for an extended period of time, chemotherapeutic medications can be held even if other starting criteria are met. During Consolidation II, all attempts should be made to continue asparaginase, unless otherwise contraindicated; if held for life-threatening illness, asparaginase should be resumed as soon as possible. Other agents (vincristine, steroid, 6MP, methotrexate, doxorubicin/dexrazoxane, IT chemotherapy) may be added back in stepwise fashion as tolerated. Weekly methotrexate may be substituted for doxorubicin in HR/VHR patients, but doxorubicin should be restarted in place of methotrexate as soon as possible. All such modifications must be discussed with and approved in advance by Lewis Silverman, MD, or designee.

If a patient has protracted myelosuppression during Consolidation II/Continuation (start of cycle delayed > 3 weeks due to low blood counts), vincristine and dexamethasone pulses can be given every 3-weeks while awaiting count recovery only with prior approval of Lewis Silverman, MD, or designee. In cases of protracted myelosuppression, a diagnostic marrow aspirate/biopsy is recommended prior to initiation of vincristine/dexamethasone pulses.

5.1.7 **Remission Induction: Dose Modifications**

- Doxorubicin: If hyperbilirubinemia at Day 4, see **Special Circumstances**
- Prednisone: All attempts should be made to avoid modifying or holding any doses. Medically treat hypertension and ketotic hyperglycemia.
- Vincristine: All attempts should be made to avoid delaying or modifying dose. A dose of vincristine may be delayed for up to 3 days for ileus, SIADH, vocal cord paralysis, cranial neuropathy or life-threatening illness; if vincristine dose is held more than 3 days for toxicity, that week's dose should be held altogether and not made up. After delay or missed dose, vincristine should be given at 100% dose (no dose reduction); dose reductions are allowed if discussed in advance with Principal Investigator or designee. If days of administration are changed, the interval between any two vincristine doses should not be less than 6 days. If direct bilirubin > 3.0 mg/dl (51.3 micromoles/L), hold dose of vincristine. With a bilirubin at this level, it may be allowable under certain circumstances to administer vincristine at 50% dose but only with prior approval of Principal Investigator.
- Methotrexate Do not give dose if patient has effusions, ascites, other fluid collections, or creatinine above normal limits for age.
- Asparaginase:
- Hold for clinical pancreatitis, deep venous thrombosis.
 - Allergic Reaction to Induction Dose of PEG asparaginase (Oncaspar or SC-PEG): Stop infusion for clinical hypersensitivity reaction. Patient should be switched to Erwinia asparaginase for all future doses of asparaginase.
 - If hypersensitivity reaction occurs within first 30 minutes of asparaginase infusion during induction phase, then patient should receive four doses of Erwinia twice-weekly during the induction phase. Dose of Erwinia: 25000 IU/m², given IM. First dose of Erwinia should be given sometime between Days 8-11 of induction, if possible.
 - If hypersensitivity reaction to PEG asparaginase occurs in the at or after 30 minutes of the asparaginase infusion has been completed, no doses of Erwinia should be given during induction phase; Erwinia asparaginase should commence with 1st post-induction asparaginase dose (CNS Phase for SR/HR patients, Consolidation IC for VHR patients).

Intrathecal Therapy:

- If patient has moderate/severe mucositis on Day 18, omit IT Methotrexate (give IT cytarabine/hydrocortisone only)
- Do not hold or modify doses of Intrathecal Cytarabine for mucositis or blood counts. If patient had previous neurologic toxicity attributed to intrathecal cytarabine, subsequent doses may be held after discussion with Lewis Silverman, MD, or designee.
- If patient has any mucositis on Day 32, do not perform lumbar puncture and do not administer ITM (or proceed to Consolidation I) until recovered. BM aspirate and biopsy may still be performed.

Mucositis Criteria:

- Mild = red mucosa - no open ulcers
- Moderate = open sores, but taking p.o. normally
- Severe = open sores associated with decreased p.o. and/or increased salivation

5.1.8 **Consolidation I (SR/HR) and Consolidation IA (VHR): Dose Modifications**

5.1.8.1 **Mucositis:**

- **Start of cycle:** If mucositis evident prior to beginning Consolidation I, hold start of cycle until mucositis has significantly improved or resolved. If anticipated delay due to mucositis is likely to be 7 or more days, may give vincristine 1.5 mg/m²/dose (maximum dose 2 mg) IV push or IV via minibag weekly until mucositis resolved (as long as no constipation or significant neuropathy).
- **During cycle:** Hold 6 MP for moderate/severe mucositis developing during Consolidation I/IA and do not re-start within the cycle.

5.1.8.2 **Creatinine elevated above normal for age:**

If creatinine elevated above upper limit of normal for age prior to start of cycle, hold high dose methotrexate. Proceed with remainder of chemotherapy. Attempt to give full cycle of Consolidation I/IA in 3 weeks if creatinine level has normalized. If still not normalized, proceed to next scheduled phase of chemotherapy. For patients who do not receive high-dose methotrexate during Consolidation I/IA, it may be given during Consolidation II (weekly MTX should not be given during a Consolidation II cycle in which HD MTX is given). Note: High dose methotrexate should not be given during Consolidation II if patient has received cranial radiation during the CNS phase.

5.1.8.3 **Edema/ascites/effusions:**

If present at start of cycle, and considered significant by treating physician, then high dose methotrexate should be held. Follow guidelines for elevated creatinine.

5.1.8.4 **Low Blood Counts:**

Hold 6MP if APC < 500 or platelets < 50K during cycle and do not re-start within the cycle.

5.1.8.5 **Abnormal Liver Function Tests:**

Hold 6MP if SGOT > 8x normal or direct bilirubin > 1.4 mg/dL (23.9 micromoles/L), during cycle.

5.1.9 **Consolidation IB: Dose Modifications (VHR Patients)**

5.1.9.1 **Low Blood Counts:**

Hold 6MP if APC < 500 or platelets < 50K during cycle and do not re-start. Delay cytarabine if APC < 500 or platelets < 50K on Day 9 (when 2nd 4-day course is due to begin), and begin this 4-day course once APC ≥ 500 and platelets ≥ 50K. Once a 4-day course of cytarabine commences, give all 4 doses of that course regardless of blood counts. If Day 9 cytarabine cannot be given within 14 days from when it was initially due because of low blood counts, it should be omitted from cycle.

5.1.9.2 **Abnormal Liver Function Tests:**

Hold 6MP if SGOT > 8x normal or direct bilirubin > 1.4 mg/dL (23.9 micromoles/L) during cycle and do not restart within the cycle. Hold Day 9 cytarabine if direct bilirubin > 1.4 mg/dL (23.9

micromoles/L) on the day it is due; administer at full dose once direct bilirubin is ≤ 1.4 mg/dL (23.9 micromoles/L). If Day 9 cytarabine cannot be given within 14 days from when it was initially due because of hyperbilirubinemia, it should be omitted from cycle.

5.1.9.3 **Mucositis:**

Hold 6MP for moderate/severe mucositis and do not restart within the cycle. Hold Day 9 cytarabine if moderate/severe mucositis on the day it is due; administer at full dose once mucositis improves. If Day 9 cytarabine cannot be given within 14 days from when it was initially due because of mucositis, it should be omitted from cycle.

5.1.10 **Consolidation IC (VHR Patients)**

5.1.10.1 **Etoposide:** Slow infusion rate in case of hypotension. Premedication with diphenhydramine, corticosteroids, and acetaminophen allowed if hypersensitivity reaction. Doses can only be held if discussed in advance with Lewis Silverman, MD or designee.

5.1.10.2 **Asparaginase:** For dose modifications due to toxicity, refer to Section 5.1.12.5

5.1.11 **CNS Treatment Phase: Dose Modifications**

5.1.11.1 **Intrathecal medications:**

- **Attempt to avoid dose reduction by re-evaluating patient in 2-3 days**
- If APC <500 or PLT <50K and/or moderate mucositis (open sores-red mucosa, but taking p.o. normally), decrease methotrexate dose in IT therapy by 50%.
- If APC <300 or PLT <25K and/or severe mucositis (decreased p.o. and increased salivation, mucosal ulcers), omit IT methotrexate and administer IT cytarabine and hydrocortisone
- If SGOT > 8 x normal and/or direct bilirubin > 1.4 mg/dL (23.9 micromoles/L): omit IT methotrexate and administer IT cytarabine and hydrocortisone.

5.1.11.2 **6- mercaptopurine:**

Hold for APC <500 or PLT <50K, SGOT > 8 x normal, direct bilirubin > 1.4 mg/dL (23.9 micromoles/L) and/or moderate/severe mucositis. Do not restart within cycle once held.

5.1.11.3 **Asparaginase:** Refer to Section 5.1.12.5.

5.1.11.4 Vincristine:

- Hold vincristine for severe constipation or neuropathy that is not responsive to maximum supportive care.
- Hold vincristine for cranial nerve abnormalities (such as ptosis).

5.1.12 Consolidation II and Continuation Therapy: Dose Modifications

5.1.12.1 Modifications for Blood Counts

Desired Hematologic Nadirs:

- o APC 500 - 750/mm³, and
- o Platelets 50,000 - 100,000/mm³.

Dose intensity is important and any delays in chemotherapy should be as short as possible.

If APC < 500 or Platelets < 50,000 during cycle (weeks 2 and 3):

- Consider holding Trimethoprim/sulfamethoxazole (Bactrim) and/or other potentially myelosuppressive, non-chemotherapeutic agents prior to reducing doses of any chemotherapy.
- Hold methotrexate and 6-MP for remainder of cycle if APC < 500 or platelets < 50,000. Do not make up missed doses of methotrexate and 6-MP. At the start of next cycle, consider reducing doses of myelosuppressive chemotherapy. Suggested adjustments: reduce both agents by 20% at start of the next cycle.
- Consider testing for TPMT (thiopurine methyltransferase) activity and/or mutation status for patients with excessive or protracted myelosuppression. If low TPMT activity and/or mutation identified, 6MP should be dose-reduced preferentially over methotrexate.
- It is suggested that Doxorubicin doses should be reduced by 20% only if an initial reduction of 6-MP does not prevent further cycles with nadirs that are too low. If doxorubicin is dose-reduced, dexrazoxane should be dose-reduced to keep ratio of dexrazoxane:doxorubicin = 10:1. **Doxorubicin Dose may be reduced by 20% only once!** There are no further dose reductions of doxorubicin if patient is already receiving 80% dose doxorubicin.
- Asparaginase should be given regardless of blood counts.

If APC < 750 or platelets < 75 K when cycle is due:

- Consider holding Trimethoprim/sulfamethoxazole (Bactrim) and/or other potentially myelosuppressive, non-chemotherapeutic agents prior to reducing doses of any chemotherapy.
- Hold all chemotherapy except asparaginase until criteria are met to start cycle. At the start of next cycle, consider reducing the doses of myelosuppressive chemotherapy. Suggested adjustments: reduce methotrexate, 6MP, and/or doxorubicin as above.
- It is suggested that Doxorubicin doses should be reduced by 20% only if appropriate reduction of 6-MP does not prevent delayed cycles or nadirs that are too low. If doxorubicin is dose-reduced, dexrazoxane should be dose-reduced to keep ratio of dexrazoxane: doxorubicin = 10:1. **Doxorubicin Dose may be reduced by 20% only once!** There are no further dose reductions of doxorubicin if patient is already receiving 80% dose doxorubicin.
- Asparaginase should be given regardless of blood counts.

If nadirs too high: Consider dose escalation of 6MP/methotrexate (doxorubicin should not be dose-escalated).

- Suggested dose escalation: Increase dosages of methotrexate and 6-mercaptopurine in 20% increments according to patient tolerance. Consider escalating only agent per cycle, alternating which agent is escalated in successive cycles.
- Dosages of 6-MP should not exceed 150% (75 mg/m²/day for 14 days).
- Maximum weekly dose of methotrexate:
 - Standard Risk and non-irradiated High Risk: 150% dose (45 mg/m²/dose)
 - High Risk with prior cranial radiation and all Very High Risk: 133% dose (40 mg/m²/dose)
- If Doxorubicin was previously reduced, dose may be escalated back to 100% if nadirs exceed goal nadirs. Doxorubicin dose should not exceed 100% (30 mg/m²/dose).

5.1.12.2 **Abnormal LFT's:**

- Hold start of cycle if SGOT (AST) >8 times normal or direct bilirubin >1.4mg/dl (23.9 micromoles/L). Begin cycle when levels have fallen below these values. (SGPT/ALT is not a criterion)
- Suggested dose adjustment of chemotherapy for abnormal LFT's:
 - high risk/very high risk patients (Consolidation II): reduce 6-MP by 20%. If elevation of SGOT/direct bilirubin recurs, then reduce doxorubicin by 20%. If doxorubicin is dose-reduced, dexrazoxane should be dose-reduced to keep ratio of dexrazoxane: doxorubicin = 10:1. **Doxorubicin Dose may be reduced by 20% only once!** There are no further dose reductions of doxorubicin if patient is already receiving 80% dose doxorubicin. If elevation of SGOT/direct bilirubin recurs with 80% dose doxorubicin, continue to reduce doses of 6-MP with subsequent cycles by 20% each cycle.
 - standard risk patients (Consolidation II): reduce methotrexate by 20%. If elevation of SGOT/direct bilirubin recurs, then reduce 6-MP by 20% with

subsequent cycles. Alternate 20% reductions of methotrexate and 6-MP with subsequent cycles if elevation of SGOT/direct bilirubin recurs.

- continuation therapy (all patients): same as standard risk patients during intensification (above).
- Consider Re-escalation of chemotherapy as tolerated if LFTs remain within normal range on dose-reduced chemotherapy after 1 or more cycles (suggested escalation by 20% increments).
- If SGOT (AST) >8 times normal or a direct bilirubin >1.4mg/dl (23.9 micromoles/L), during cycle, hold 6-MP and methotrexate. These drugs may be resumed during the same cycle or at the start of the next cycle when levels have fallen below these values. Do not make up missed doses. Consider dose reductions when agents are resumed. Suggested adjustments: reduce doses of these agents as suggested above when they are resumed (and reduce doxorubicin at the start of then next cycle if patient receiving this agent). Do not make up missed doses of 6MP/methotrexate.
- Asparaginase should be given regardless of SGOT (AST). **Hold asparaginase if direct bilirubin is > 1.4 mg/dL (23.9 micromoles/L). Restart asparaginase without dose modification once direct bilirubin is $\leq$ 1.4 mg/dL (23.9 micromoles/L).**

5.1.12.3 Mucositis

mild = red mucosa - no open ulcers

moderate = open sores, but taking p.o. normally

severe = open sores associated with decreased p.o. and/or increased salivation

- Hold start of cycle for moderate/severe mucositis. When mucositis resolves, begin cycle, consider reducing doses of methotrexate/6-MP/doxorubicin as suggested above for abnormal LFTs (depending on risk group and phase of therapy).
- Hold week 2 or 3 methotrexate for moderate/severe mucositis. Restart when mucositis resolves. May restart during the same cycle or at the next of the cycle. Consider reducing doses when methotrexate restarted (suggested: 20% dose reduction). Do not make up missed doses of methotrexate.
- Hold 6-MP for severe mucositis. Restart when mucositis resolves. May restart during the same cycle or at the start of the next cycle. Consider reduced doses when restarting (suggested: 20% dose reduction). Do not make up missed doses of 6-MP.
- If patient has recurrent mouth sores, consider evaluation for HSV and prophylactic acyclovir.

5.1.12.4 Cardiac Studies

- Hold doxorubicin if patient has symptomatic congestive heart failure. Do not restart.
- Asymptomatic echocardiographic changes (eg, decreased shortening fraction or ejection fraction): Call Principal Investigator, Lewis Silverman, MD or designee to discuss management. Doxorubicin may be held for asymptomatic abnormal echocardiogram after discussion with Principal Investigator or designee, and may be restarted if shortening fraction or ejection fraction improves.

5.1.12.5 Asparaginase

- Patient should be observed after asparaginase dose as per institutional practice for possible allergic reaction.
- Clinical Hypersensitivity: Symptoms may include rash, urticaria, lip/tongue swelling, respiratory symptoms, wheezing, hypotension

For any clinical hypersensitivity reaction to SC-PEG asparaginase or Oncaspar:

Switch to twice-weekly Erwinia IM (intramuscular). Dose of Erwinia: 25,000 IU/m² IM twice weekly.

- If a patient is unable to tolerate Erwinia IM due to behavioral issues or pain related to frequent IM injections, Erwinia IV (intravenous) may be administered. **Dose of IV Erwinia: 25,000 IU/m² IV 3x/ week** (Monday, Wednesday, Friday), infused in 100 mL of normal saline over 1 hour. Once a patient has switched to IV Erwinia, they may not be switched back to IM Erwinia **The first dose of IM Erwinia should be administered approximately one week (or as soon as feasible) after the dose of Oncaspar or SC-PEG that caused the hypersensitivity reaction.**
- A PK sample should be obtained on the day of the first Erwinia dose, just prior to administration.
- If Erwinia dose is held or delayed, the PK should be collected prior to the correct corresponding asparaginase dose number (not by the week number).
- Direct bilirubin should be checked once per week in patients receiving Erwinia asparaginase. Bilirubin does not need to be checked prior to each dose of Erwinia.
- Calculation of number of doses of Erwinia to be given:
 - For patients randomized to IV SC-PEG (intended to receive 10 post-induction doses of SC-PEG): 6 doses (3 weeks) of IM Erwinia (given twice-weekly) replaces each dose of IV SC-PEG
 - Total # IM Erwinia doses to be administered= 6 x total # of remaining post-induction doses of SC-PEG the patient would have received (ie, 10 minus the # doses of post-induction SC-PEG doses that a patient has already received)
 - For IV Erwinia: 9 doses given 3 x weekly in 100 mL of normal saline over 1 hour (3 weeks) replace each dose of IV SC-PEG. Total # IV Erwinia doses to be administered= 9 x total # of remaining post-induction doses of SC-PEG the patient would have received (ie, 10 minus the # doses of post-induction SC-PEG doses that a patient has already received)
 - Note: Be sure to take into account the IM Erwinia doses and subtract them when doing the calculation of number of doses of IV Erwinia to be given.

- o For patients randomized to IV Oncaspar (intended to receive 15 post-induction doses of Oncaspar): 4 doses (2 weeks) of IM Erwinia (given twice-weekly) replaces each dose of IV Oncaspar
 - Total # IM Erwinia doses= 4 x total # of remaining post-induction doses of Oncaspar the patient would have received (15 minus the # doses of post-induction Oncaspar doses that a patient has already received)
 - For IV Erwinia: 6 doses give 3x weekly in 100 mL of normal saline over 1 hour (2 weeks) replace each dose of IV Oncaspar. Total # Erwinia doses= 6 x total # of remaining post-induction doses of Oncaspar the patient would have received (15 minus the # doses of post-induction Oncaspar doses that a patient has already received)
 - Note: Be sure to take into account the IM Erwinia doses and subtract them when doing the calculation of number of doses of IV Erwinia to be given.
- o If hypersensitivity reaction to SC-PEG or Oncaspar occurred within first 30 minutes of infusion, that dose is not included in the total # of post-induction asparaginase doses a patient has already received
- o If hypersensitivity reaction to SC-PEG or Oncaspar occurred 30 minutes or more after the infusion began, then that dose should be counted as an administered post-induction dose when calculating the # of post-induction asparaginase doses a patient has already received.
- If patient develops clinical hypersensitivity to Erwinia, asparaginase is discontinued
- If Erwinia is unavailable, asparaginase is discontinued.

Silent Allergy: If after the first post-induction dose of asparaginase is administered (during Consolidation IC, CNS or Consolidation II), patient has 2 consecutive NSAA levels that are non-detectable (<0.025 IU/mL), then patient will be considered to have silent inactivation and will be switched to twice-weekly IM Erwinia asparaginase. IM Erwinia should be administered as described above for patients with clinical hypersensitivity. The first dose of Erwinia IM should be administered approximately one week (or as soon as feasible) after the last dose of asparaginase.

Note: A non-detectable pre-dose level will only be considered to be consistent with silent inactivation if the level was obtained prior to an asparaginase dose which had been administered without any delay from protocol-proscribed intervals (ie, 2-weeks between Oncaspar doses and 3-weeks between SC-PEG doses). Levels that are obtained more than 3 days after proscribed intervals may not be used for determination of silent inactivation.

Inform pharmacy at time of allergic reaction that preparation will be switched with the next dose of asparaginase. A PK sample should be obtained on the day of the first IM Erwinia dose, just prior to administration.

Calculation of number of doses of Erwinia to be given for patients with silent allergy:

- The goal is for patients to receive a total of 30 weeks of asparaginase depletion during post-induction therapy.
- If patients have never had any detectable nadir asparaginase activity levels after post-induction treatment doses, then they should receive 30 weeks of Erwinia asparaginase after silent allergy/inactivation is identified.
- If patient had detectable nadir asparaginase activity levels after post-induction doses of either Oncaspar or SC-PEG prior to the development of silent allergy/inactivation, then those doses may be counted as “effective” asparaginase doses, and the number of weeks following those doses should be taken into account when determining how many weeks of Erwinia asparaginase should be given to total 30 weeks. For instance:
 - If 2 weeks after the 1st post-induction dose of Oncaspar, patient had a detectable nadir asparaginase activity level, but then did not have any detectable nadir levels after subsequent doses, then the patient should receive 28 weeks of Erwinia asparaginase (30 total weeks-2 weeks of “effective” asparaginase after the first dose of Oncaspar)
 - If 3 weeks after the 1st post-induction dose of SC-PEG, patient had a detectable nadir asparaginase activity level, but then did not have any detectable nadir levels after subsequent doses, then the patient should receive 27 weeks of Erwinia asparaginase (30 total weeks-3 weeks of “effective” asparaginase after the first dose of SC-PEG)

If Erwinia is used after determination of silent inactivation, give 25,000 IU/m² IM twice weekly to complete 30 weeks of asparaginase therapy.

- If clinical hypersensitivity reaction develops to Erwinia, asparaginase is discontinued.
- If Erwinia is unavailable, asparaginase is discontinued.

IV Erwinia (3x/week) may be used instead of IM Erwinia if patient unable to tolerate IM injections due to behavioral problems or pain, as described above for clinical hypersensitivity. Give 25,000 IU/ m² IV 3x/week to complete 30 weeks of asparaginase therapy. Infuse IV Erwinia in 100 mL of normal saline over 1 hour.

- CNS events (bleed, thrombosis, infarction): Hold asparaginase. Resume when all clinical symptoms have resolved (and evidence of recanalization on CT/MRI in case of thrombus). In cases of significant CNS events, asparaginase may be permanently held after discussion with Dr. Lewis Silverman or designee.
- Deep vein thrombosis: Hold asparaginase. Begin treatment with anticoagulant medication. Resume asparaginase after coagulation status stabilized and clinical symptoms have resolved. If recurrent DVT on anticoagulation after restarting asparaginase, hold permanently.

- Lipemic Blood: Triglyceride levels do not need to be routinely followed for patients receiving asparaginase. If triglyceride levels are monitored, fasting levels are preferable. Hold asparaginase if a patient is found to have a triglyceride level >2000 mg/dl (>22.8 mmol/L). When triglyceride level drops below this level, resume asparaginase therapy without dose modification. For recurrent hypertriglyceridemia, lipid-lowering agents may be used at discretion of treating clinician.
- Severe pancreatitis (abdominal pain with amylase or lipase elevation above institutional normal limits for ≥ 72 hours duration and/or development of pancreatic pseudocyst or life-threatening complication): Permanently stop asparaginase.
- Mild to moderate pancreatitis (defined as abdominal pain of <72 hours duration with amylase and/or lipase elevation): Hold asparaginase. Resume when signs, symptoms and laboratory values return to baseline. Asparaginase may be discontinued after recurrent episodes of mild/moderate pancreatitis. Please call Principal Investigator, Lewis Silverman, MD or designee to discuss.
- Asymptomatic hyperamylasemia (for patients with amylase elevation ≥ 3 x upper limit of normal, but no abdominal pain): If no concurrent cranial radiation, hold asparaginase for elevated amylase level (≥ 3 X normal), and resume when level normalizes. For patients receiving cranial radiation, check lipase level if amylase is elevated but patient is asymptomatic; if lipase elevated above normal, hold asparaginase. Resume when laboratory values normalize. If lipase within normal limits when patient is receiving cranial radiation, do not hold asparaginase.
- Elevated Direct bilirubin: Hold asparaginase if direct bilirubin is > 1.4 mg/dl (23.9 micromoles/L). Restart asparaginase without dose modification once direct bilirubin is ≤ 1.4 mg/dl (23.0 micromoles/L).
- Asparaginase Intolerance: For patients who are unable to receive more than 10 weeks of asparaginase (due to allergy to all preparations, severe or recurrent pancreatitis, other severe toxicities):
 1. Standard Risk patients at the start of the next 3-week cycle, patient should receive 3 cycles of High Risk Consolidation II chemotherapy (that is, three cycles with doxorubicin + dexrazoxane instead of weekly methotrexate, higher dose dexamethasone, as well as vincristine and 6MP), so that cumulative dose doxorubicin is $150 \text{ mg/m}^2 \pm 15 \text{ mg/m}^2$ then proceed to Continuation Therapy. Dexrazoxane should be given prior to doxorubicin, as specified in High risk Consolidation II chemotherapy.
 2. High Risk/Very High Risk patients: Hold asparaginase. Continue Consolidation II chemotherapy until completion of doxorubicin ($300 \text{ mg/m}^2 \pm 15 \text{ mg/m}^2$) and 10 post-induction chemotherapy cycles with high dose dexamethasone ($18 \text{ mg/m}^2/\text{day} \times 5 \text{ days}$), then proceed to Continuation Therapy.

5.1.12.6 Vincristine

- Hold vincristine for severe constipation or neuropathy that is not responsive to maximum supportive care. Suggested guidelines for reintroducing vincristine: Re-introduce at 50% dose when patient is improved, and escalate in 25% increments to 100% dose as tolerated.

- Hold vincristine for cranial nerve abnormalities. Reintroduce when improved or resolved. Suggested guidelines for reintroducing vincristine as above.
- For mild neuropathy (such as gait abnormalities or parasthesias), vincristine may be dose-reduced instead of held, as per discretion of treating physician. Attempt to dose escalate when symptoms improve.
- If direct bilirubin > 3.0 mg/dl (51.3 micromoles/L), hold dose of vincristine. With a bilirubin at this level, it may be allowable under certain circumstances to administer vincristine at 50% dose but only with prior approval of Principal Investigator.

5.1.12.7 **Dexamethasone**

- Severe steroid withdrawal symptomatology (myalgias, arthralgias, etc) may be treated with a taper. Total dose of steroid received per cycle (including taper) should not exceed total dose indicated in protocol (that is 5-day total of steroid). Suggested initial taper: use a 4-day full course followed by 2-3 day rapid taper. For severe withdrawal symptomatology in HR/VHR patients that persists despite taper and pain medications, lower (SR) dosing of dexamethasone (6 mg/m²/day, with or without taper) during Consolidation II may be used at discretion of treating clinician.
- For symptomatic avascular necrosis (osteonecrosis), permanently stop steroids. Steroids should only be discontinued in patients who have both symptoms (eg, bone or joint pain) with confirmatory radiographic findings (eg, plain film, MRI). Steroids should not be permanently discontinued for asymptomatic radiographic changes found incidentally on radiographic studies unless approved in advance by Principal Investigator.
- For bone fractures, hold corticosteroid until fractures are healed, then resume without dose modification. Do not make up missed doses. Healing may be documented by radiographic changes, symptomatic improvement or clearance by an orthopedist. For vertebral compression fractures or other fractures for which healing is not easily documented by radiographs, resolution of symptoms (eg, pain) may be used as a sign of healing.
- Steroids may be held at discretion of treating physician after episode of pancreatitis. All attempts should be made to reintroduce steroids as soon as possible. Do not make up missed doses.
- For HR/VHR patients who experience severe behavioral or mood changes during Consolidation II, dose reduction to SR dose is allowed. For severe behavioral or mood changes for patients receiving SR dose of corticosteroids, corticosteroids may be stopped or given less frequently only after discussion with Lewis Silverman, MD or designee.
- Rarely, preparation may be changed to prednisone for intolerable side effects. If changed, change preparation as follows:
 - If patient receiving dexamethasone 6 mg/m²/day, change to prednisone 40 mg/m²/day divided twice daily for five days on week 1 of each cycle.
 - If patient receiving dexamethasone 18 mg/m²/day, change to prednisone 120 mg/m²/day divided twice daily for five days on week 1 of each cycle.

Principal Investigator or designee must be contacted for prior approval of such a change.

5.1.12.8 **IT Chemotherapy**

- IT chemotherapy may be modified or held in case of seizures (attributable to prior IT chemotherapy), leukoencephalopathy, or other significant neurologic complications. IT methotrexate may be held (IT ara-C/hydrocortisone given instead) or all IT chemotherapy may be delayed or held for such conditions. All such changes in IT chemotherapy must be discussed in advance with Principal Investigator, Lewis Silverman, MD, or designee.

CLINICAL RESPONSE CRITERIA

5.2 Definition of CNS Status

CNS-1 = CSF without blasts on cytopsin, regardless of CSF WBC count

CNS-2 = CSF WBC <5 with blasts present on cytopsin

CNS-3 = CSF WBC ≥ 5 with blasts present on cytopsin

Steinherz/Bleyer Algorithm to Interpret Traumatic LP's (>10 RBC per high power field) with ≥ 5 WBC/hpf:

- CSF specimens with > 10 RBC/hpf and ≥ 5 WBC/hpf should be treated as CNS-3 if : (CSF WBC/CSF RBC) > 2x (Blood WBC/Blood RBC).
- All other CSF specimens with > 10 RBC/hpf and ≥ 5 WBC/hpf in CSF specimen should be treated as CNS2.

5.3 Definition of Complete Remission

5.3.1 Leukemia:

An interpretable bone marrow (a specimen with normal marrow elements present) with fewer than 1% malignant lymphoblasts by microscopic examination and peripheral blood without lymphoblasts, and an APC $\geq 1000/\text{mm}^3$ and platelets $\geq 100,000/\text{mm}^3$, and no evidence of extramedullary leukemia (no blasts in spinal fluid, at least 70% reduction in size of masses noted on imaging at diagnosis, as defined below for patients with lymphoblastic lymphoma). Note: Patients are allowed to have $\geq 1\%$ normal myeloid or lymphoid blasts (hematogones) in their marrow consistent with recovery and still meet the definition of complete remission. Normal recovery blasts may be distinguished from persistent malignant lymphoblasts by flow cytometry, immunohistochemistry or other studies. Consult principal investigator with any questions.

5.3.2 Lymphoblastic Lymphoma:

At least a 70% reduction in size of largest nodes or masses noted at diagnosis. Reduction may be measured as a decrease in a sum of the products of the two greatest diameters (SPD) of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features:

- a) they should be clearly measurable in at least two perpendicular dimensions,
- b) they should include mediastinal masses whenever this site was initially involved.

In addition to this radiographic criterion, there should also be complete disappearance of all clinical evidence of disease by physical examination and no morphologic evidence of disease in bone marrow (if involved at initial diagnosis) and spinal fluid.

5.4 Failure to Achieve Remission (Induction Failure)

5.4.1 Leukemia:

If $\geq 1\%$ blasts (confirmed to be leukemic lymphoblasts by flow cytometry, immunohistochemistry or other studies) are identified in the marrow on Days 32, or on any marrow performed up through Day 53 (without a preceding marrow consistent with complete remission), the patient will be classified as an Induction Failure and removed from protocol (contact Principal Investigator or designee prior to removing from protocol if patient is induction failure). Any patient with evidence of extramedullary leukemia on exam, in the spinal fluid or by radiographic imaging ($< 70\%$ reduction in size of largest nodes or masses noted at diagnosis, or any new biopsy-proven masses) will also be considered an induction failure, regardless of marrow findings.

5.4.2 Lymphoblastic Lymphoma:

If end-induction imaging reveals persistent nodal involvement or masses ($< 70\%$ reduction in size of largest nodes or masses noted at diagnosis), the patient will be classified as an Induction Failure and removed from protocol (Notify Principal Investigator or designee if patient is an induction failure). Any patient with new, biopsy-proved sites of disease will also be considered an induction failure. In addition, any patient with evidence of persistent disease in bone marrow ($\geq 5\%$ blasts confirmed by flow cytometry, FISH or other studies) or spinal fluid (CNS-3) will also be considered an induction failure.

5.5 Criteria for relapse

5.5.1 Greater than 5% lymphoblasts identified morphologically in bone marrow aspirate/biopsy identified to be leukemic by flow cytometry, cytogenetics, FISH, immunohistochemistry, or other tests.

5.5.2 Development of biopsy-proven extramedullary site of disease (eg, CSF, testicle, lymph node)

5.5.2.1 CNS relapse: CSF sample with ≥ 5 WBC per high power field and lymphoblasts on cytopspin, or 2 consecutive CSF specimens meeting the definition of CNS-2 (< 5 WBC/hpf with lymphoblasts seen) obtained at least 3 weeks apart.

6. STATISTICAL CONSIDERATIONS

Patients will be randomized to receive either IV Calaspargase Pegol (SC-PEG) 2500 IU/m² (arm A) or IV Oncaspar 2500 IU/m² (arm B), both administered as a single dose during induction and then for 30 weeks during post-induction treatment phases (IV SC-PEG given every 3 weeks and IV Oncaspar every 2 weeks). Samples to assess serum asparaginase enzyme activity will be obtained weekly (for 4 weeks) after the induction dose (days 4, 11, 18, and 25 post-asparaginase dose). In the post-induction treatment phases, IV SC-PEG 2500 IU/m² will be administered every 3 for 30 weeks (weeks 1, 4, 7, 10, 13, 16, 19, 22, 25 and 28, a total of 10 doses in 30 weeks) with samples obtained prior to every dose. IV Oncaspar 2500 IU/m² will be administered every two weeks on weeks 1,3,5,...29 (a total of 15 doses in 30 weeks) and asparaginase enzyme samples will be obtained prior to every dose. Both IV Oncaspar and IV SC-PEG asparaginase enzyme level samples will be taken at the same time point on weeks 7, 13, 19 and 25.

Safety data will be monitored on each arm and compared to that of the historical control rate observed on DFCI protocol 05-001. On DFCI Protocol 05-001, 7% of enrolled subjects were not randomized due to ineligibility, induction failure, induction death, early toxicity, early withdrawal, and the presence of the Philadelphia chromosome. Additionally, some patients will be unable to complete 30 weeks of post-induction therapy. Therefore, we assume that approximately 7% of patients who enroll on this randomized pilot trial will not be evaluable for post-induction toxicity assessment and the post-induction pharmacokinetic analyses.

6.1 Primary Objectives: Safety and Feasibility of SC-PEG asparaginase

A total of 240 patients will be enrolled on this trial to evaluate the primary endpoint. We plan to enroll 120 patients on each arm to have 112 patients on each arm evaluable for the monitoring of asparaginase toxicity in Consolidation I, CNS and Consolidation II phases of treatment and the pharmacokinetic secondary endpoint. The randomization will be stratified into four groups based on disease type, age and risk group classification: ALL patients under 10 years of age and SR, ALL patients under 10 years of age and HR, ALL patients 10 years and older (and by definition HR), and patients with lymphoblastic lymphoma. We estimate that of the 240 patients enrolled, 34 will have lymphoblastic lymphoma.

6.1.1 Safety

16.1.1.1 Safety Monitoring

One primary objective of this study is to compare the asparaginase-related toxicity rate of IV SC-PEG with that of IV Oncaspar on Protocol 05-001. The toxicity data from the IV Oncaspar arm of this study will be monitored to ensure that the rate of asparaginase-related toxicities with IV Oncaspar is not dissimilar between Protocol 05-001 and Protocol 11-001, thus allowing for the toxicity comparison between 11-001 IV SC-PEG- and 05-001 IV Oncaspar-treated patients . Toxicity rates from the induction phase and post-induction phases of treatment for both arms will be monitored.

We will carefully monitor and prospectively collect data relating to asparaginase-related toxicities of any grade. On DFCI Protocol 05-001, the three most common asparaginase-related toxicities were pancreatitis, hypersensitivity and thrombotic complications. The rates of these toxicities on each arm will be compared at the DMC meeting approximately every six months. We will also monitor other severe toxicities, defined as any grade 4 or higher toxicity (excluding asymptomatic laboratory abnormalities, and noting that elevations of amylase and lipase are markers of pancreatitis and will be included in the rate of asparaginase-related toxicity) occurring during the induction phase and during the 30 weeks of post-induction treatment including asparaginase. Severe pancreatitis will be defined as an elevation in serum amylase greater than three times normal with clinical signs and symptoms consistent with that diagnosis persisting for more than 72 hours. Mild to moderate pancreatitis will be defined as above with signs and symptoms lasting for less than 72 hours. All other toxicity grading will be per CTC version 4.0.

On DFCI Protocol 05-001, the overall asparaginase-related toxicity rate for patients randomized to IV Oncaspar was 27% for the Consolidation I, CNS and Consolidation II phases of treatment. Safety data will be subsequently monitored approximately every 6 months by the DMC. The safety analysis will not be a comparison of randomized arms, but each arm will be monitored by comparing toxicity rates to the historical control arm of IV Oncaspar on 05-001. We will monitor the proportion of patients experiencing asparaginase-related toxicity to ensure that this rate does not significantly differ from the 27%, observed on 05-001 in either arm. Assuming we have approximately 30 patients enrolled on each arm (60 total), who have adequate toxicity data (Consolidation I-Consolidation II phases of treatment) at the time of the first interim analysis, if 12 or more of the 30 (40%; exact two-sided 80% CI: 28%-53%) patients experience asparaginase-related toxicity, we would consider this unacceptable, as the expected rate of 27% is excluded from the lower bound of the exact one-sided binomial 90% confidence interval (or exact two-sided 80% CI). The trial would stop accrual and the safety data would be carefully reviewed by the DMC. Similar assessments will be made at each interim analysis for each arm. Based on an accrual rate of 10 patients per month and a DMC meeting occurring every six months we plan on three interim looks at the data and a final analysis at 100% information when all patients are enrolled have adequate toxicity follow-up data (approximately 10 months post consolidation I). We assume that the asparaginase-related toxicity rate will be similar for lymphoblastic lymphoma patients. With 112 evaluable patients on each arm at the final analysis, if 38 or more (34%; exact two-sided 80% CI: 28%-40%) patients experience asparaginase-related toxicity, we would consider this unacceptable. The upper bound of the exact one-sided 90% CI (or exact two-sided 80% CI) for the true unknown rate of asparaginase-related toxicity would be no more than 40%.

At each DMC meeting, we will also consider asparaginase-related toxicities separately and consider stopping if the incidence of pancreatitis, allergy, and/or thrombosis for the SC-PEG arm are significantly higher than that of IV-Oncaspar. Similarly, the induction toxicity rate for pancreatitis, allergy, thrombosis, bacterial and fungal infection and the rate of excessive toxicity (all other grade 4 or higher toxicities) will also be compared to that of the historical control rate and monitored at each DMC meeting. Since the study is not powered to detect differences in toxicity rates between arms, only to monitor rates versus historical controls, comparison of the

toxicity rates between arms will only be made at the request of the DMC at each interim analysis. The rate of asparaginase-related toxicity will be reported for each arm along with the exact binomial 90% confidence intervals with a maximum width no wider than 16%.

Toxicity grading using CTC version 4.0 will also be reported for all patients who received therapy. The number and proportion of patients with each toxicity type will be reported. The worst grade toxicity will be determined for each patient and the proportions will be reported with the 90% confidence intervals for each arm.

16.1.1.2 Minimum Residual Disease (MRD) Monitoring

COG Protocol AALL07P4 tested SC-PEG asparaginase during the induction phase. Patients were initially randomized to receive either SC-PEG or Oncaspar at 2500 IU/m². After a protocol amendment, patients randomized to SC-PEG received a dose of 2100 IU/m². The study was suspended on December 22, 2010 based on a higher rate of Day 29 end-induction MRD-positivity (MRD+) for patients treated with SC-PEG 2100 IU/m²/dose compared with SC-PEG 2500 IU/m²/dose or Oncaspar 2500 IU/m²/dose. The difference in frequency of MRD-positivity was statistically significant and crossed pre-defined safety monitoring boundaries.

Based on this finding, we will monitor the frequency of high end-induction MRD (defined as > 0.001 by PCR assay) in patients with B-precursor ALL at each interim analysis. Of the first 432 B-ALL patients treated on Protocol 05-001, end-induction MRD was successfully assayed in 92% of patients and 12.5% were found to be MRD-high. We will monitor the proportion of patients with MRD levels >0.001 in each arm at the end of remission induction to ensure that this rate does not significantly differ from 12.5%. Assuming we have 30 patients per arm (60 in total) at the first interim analysis and 92% have informative end-induction samples (N=28), if 7 or more of the 28 (25%; two-sided 80% CI: 14%-38%) patients have high MRD samples, we would consider this unacceptable, as the expected rate of 12% is excluded from the lower bound of the exact one-sided 90% confidence interval. The trial would stop accrual and the data would be reviewed by the DMC. Similar assessments will be made at each interim analysis. Comparisons between arms will be made at the request of the DMC at each interim analysis. The rate of high end-induction MRD will also be reported for each arm along with the 90% confidence intervals with a maximum width no wider than 16%.

6.1.2 Feasibility and Pharmacokinetic Endpoints

16.1.2.1 Feasibility of Every 3-Week Dosing of IV SC-PEG

The feasibility of administering IV SC-PEG at a dose of 2500 IU/m² every 3-weeks will be assessed by calculating the proportion patients who achieve a nadir serum asparaginase activity (NSAA) level ≥ 0.10 IU/mL (considered therapeutic) at any post-induction time point in each arm. We will compare the proportion of patients who have at least 1 NSAA measure ≥ 0.10 IU/mL between arms. In the first 114 analyzed on DFCI Protocol 05-001, 100% of patients treated with IV Oncaspar had at least 1 NSAA level ≥ 0.10 IU/mL during the post-induction asparaginase consolidation. With 112 evaluable patients on each arm and assuming 99% of patients on the IV Oncaspar arm have at least 1 NSAA level ≥ 0.10 IU/mL during the post-induction asparaginase consolidation, we will have 89% power to detect a 10% reduction in the proportion of patients who have at least 1 NSAA level ≥ 0.10 IU/mL during the post-induction

asparaginase consolidation, using a one-sided Fisher exact test at the 0.025 significance level. If there is no difference in the proportion of patients who have at least 1 NSAA level ≥ 0.10 IU/mL during the post-induction asparaginase consolidation, we will consider the administration of every 3-week IV SC-PEG feasible.

16.1.2.2 Asparaginase Enzyme Activity: Induction Phase – Early Stopping

We will also compare the proportion of patients with serum asparaginase enzyme activity of at least 0.10 IU/mL at 4, 11, 18 and 25 days after a single dose of either IV Oncaspar (2500 IU/m²) or IV SC-PEG (2500 IU/m²) is administered during the induction phase.

At the Day 25 time point (18 days after the dose of IV Oncaspar) on Protocol 05-001, 88% patients in induction had a serum asparaginase enzyme activity level ≥ 0.10 IU/mL, however only 7% achieved this level at the Day 32 time point. On the COG Protocol AALL07P4, 100% of patients had a serum asparaginase enzyme activity level ≥ 0.10 IU/mL at both 22 and 29 days after the dose of IV SC-PEG. Asparaginase enzyme activity will be run in real time from samples obtained at Induction Days 25 and 32 (18 and 25 days after asparaginase dose) for all patients enrolled on Protocol 11-001. Assuming we have approximately 30 evaluable patients enrolled on each arm (60 total) at the time of the first interim analysis, if 23 or fewer of the 30 (77%; exact two-sided 80% CI: 64%-87%) patients have an asparaginase enzyme activity level ≥ 0.10 IU/mL, at the Day 25 time point (on either arm), we would consider this unacceptable, as the expected rate of 88% is excluded from the upper bound of the exact one-sided binomial 90% confidence interval. Similarly, at the Day 32 time point (25 days after the dose of IV SC-PEG) if 23 or fewer of the 30 patients (77%; exact two-sided 80% CI: 64%-87%) on the IV SC-PEG arm have an asparaginase enzyme activity level ≥ 0.10 IU/mL, we would also consider this unacceptable. This stopping rule will ensure that the proportion of patients who achieve a target therapeutic level with IV SC-PEG is comparable to that of IV Oncaspar at Day 25 (18-days post-dose) and is maintained at Day 32 (25-days post-dose), which will justify the every 3-week dosing schedule during Consolidation for patients randomized to received IV SC-PEG. Similar comparisons will be made at each interim analysis and at the final analysis.

Descriptive statistics including the median, range, mean and standard deviation of asparaginase enzyme level will be reported and compared as appropriate at each induction day that samples are collected for each arm. We will analyze and compare the data between arms longitudinally as described for the post-induction time points.

16.1.2.3 Asparaginase Enzyme Activity – Consolidation Phase (post-Induction)

Both IV Oncaspar and IV SC-PEG asparaginase enzyme level samples will be collected in real time at the same post-induction time points on weeks 7, 13, 19 and 25. Descriptive statistics including the median, range, mean and standard deviation of serum asparaginase activity will be reported for each post-induction week that samples are collected for each arm. To ensure that asparaginase levels are being maintained at the ≥ 0.10 level, the proportion of samples with levels ≥ 0.025 , ≥ 0.10 , ≥ 0.20 , and ≥ 0.40 IU/mL at each time point for both arms will also be reported and reviewed at each DMC meeting.

We will directly compare asparaginase enzyme activity levels between the two arms. With a total of 224 evaluable patients (112 on each arm), we would have 96% power to detect a mean

difference of 0.15 in asparaginase enzyme activity level at the week 7 time point (estimated to be steady-state based on data from Protocol 05-001) using a two-sided t-test and assuming a standard deviation of 0.30. This is equivalent to an effect size ($\delta=\Delta/\sigma$) of 0.5.

In addition to week 7 post-induction, we will also collect asparaginase enzyme levels at weeks 13, 19, and 25 for every 2-week IV Oncaspar and compare them to every 3-week IV SC-PEG. We will compare the asparaginase enzyme levels between arms longitudinally with a random effects mixed model as appropriate. A log-10 transformation will be used for the asparaginase levels if the distribution of asparaginase enzyme levels warrant. These models will consider additional baseline patient characteristics including age sex, as well as the stratification factors of risk group and disease type, while testing for a difference in asparaginase enzyme activity between arms. Generalized estimating equation (GEE) models will be explored using cut-offs including ≥ 0.025 , ≥ 0.10 , ≥ 0.20 , and ≥ 0.40 IU/mL.

6.2 Secondary Objectives

6.2.1 Antibiotic Prophylaxis during Induction Phase

Based on historical rate of bacterial infection in the induction phase of treatment on 05-001 of 25%, we will also test the hypothesis that antibiotic prophylaxis will significantly reduce the rate of bacterial infection. We will compare the rate of infection during the induction phase in patients with ALL enrolled on Protocol 11-001 with those who were treated on Protocol 05-001. The induction regimen of the two protocols is nearly identical, with the following exceptions: 1) patients on Protocol 11-001 will receive either a single dose of IV SC-PEG or IV Oncaspar while all patients on Protocol 05001 received a single dose of IV Oncaspar and 2) patients on 11-001 will receive antibiotic prophylaxis while those on Protocol 05-001 did not. For the 11-001 patient cohort, we will only consider the infections of patients with ALL (not lymphoblastic lymphoma) in this comparison, because only patients with ALL were treated on Protocol 05001 and the frequency and severity of infections may be different in patients with lymphoblastic lymphoma who do not have marrow involvement at diagnosis (and thus may have a higher neutrophil count for longer during the induction phase).

Because of potential interaction between asparaginase type and risk of infection, we will analyze infection rates separately in each randomized arm. With approximately 103 patients on each arm (excluding lymphoma patients), we would have 82% power to detect a 12% reduction in the rate of bacterial infection in the induction phase of treatment based on a one-sample, 1-sided exact binomial test with a significance level of 0.025. Each arm will be compared to that of the historical control rate of 25%.

6.2.2 Efficacy

Although not sufficiently powered to detect difference between the arms, event-free survival (EFS) and overall survival (OS) will be calculated using the method of Kaplan and Meier for each arm. Event-free survival will be defined as the time from achievement of complete remission to the time of relapse, death or second malignancy. Patients not achieving complete remission will be considered events at time zero. Overall survival will defined as the time from diagnosis until death. Five-year estimates of EFS and OS will be provided for each arm along

with the 90% confidence intervals estimated using the formula of Greenwood once sufficient follow-up data is obtained. Additionally, we will report EFS and OS estimates for children (<10 years) and adolescents (≥ 10 years) and for lymphoblastic lymphoma patients separately for each arm along with the appropriate confidence intervals.

Since 2005, we have treated patients with VHR ALL (B-precursor patients with high end-induction MRD and/or high-risk cytogenetics) with a novel chemotherapy regimen including two additional cycles of consolidation therapy. Treatment for VHR patients on Protocol 11-001 will be identical to that on Protocol 05-001, except for the asparaginase preparation in some patients. We will combine outcome data for the VHR cohort on Protocol 11-001 with those treated on Protocol 05-001 to describe the outcome of this patient subset with the intensified VHR treatment. We estimate that approximately 70 patients will have been treated on the VHR arm on Protocol 05-001 at the time of its closure and anticipate that approximately 20 ALL patients on Protocol 11-001 will be classified as VHR for a total of 90 patients combined. Preliminary estimates of EFS and OS will be reported for this cohort of patients.