Pediatric Acute Lymphoblastic Leukemia Protocol 2008 (PALL08)

Department of Pediatric Hematology/Oncology

King Fahd National Centre for Children's Cancer and Research

King Faisal Specialist Hospital and Research Centre,

P. O. Box 3354, MBC 53

Riyadh, 11211 Saudi Arabia

Pediatric Acute Lymphoblastic Leukemia Protocol 2008 (PALL08)

Low Risk Pre B- ALL Protocol (PALL08-LR)
Modified CCG 1991 Regimen IS

High Risk Pre B-ALL Protocol (PALL08-HR)
Modified CCG 1961 Regimen C

Very High Risk Pre B-ALL Protocol (PALL08-VHR)
Modified CCG 1961 Regimen D

Contents

1.0 Introduction

Over the last ten years patients with Acute Lymphoblastic Leukemia (ALL) seen within the Leukemia Program of the Department of Pediatric Hematology/Oncology were diagnosed, risk assigned and treated in a uniform fashion. The treatment administered was based on protocols from the 1800 series of the CCG and the high risk arm of the Total XIII protocol from St. Jude Children's Research Hospital. In order to plan for further development of the ALL protocols it was essential to review the result of our current strategy.

The results of this analysis shows the 5-year overall survival (OS) for all the patients (n=404) is 79.9%, while the event free survival (EFS) is 68.7% (see Figure 1). Of the 105 first events that were recorded, 88 were relapses and 17 were deaths. These deaths constitute 4.2% of the total 404 patients evaluated.

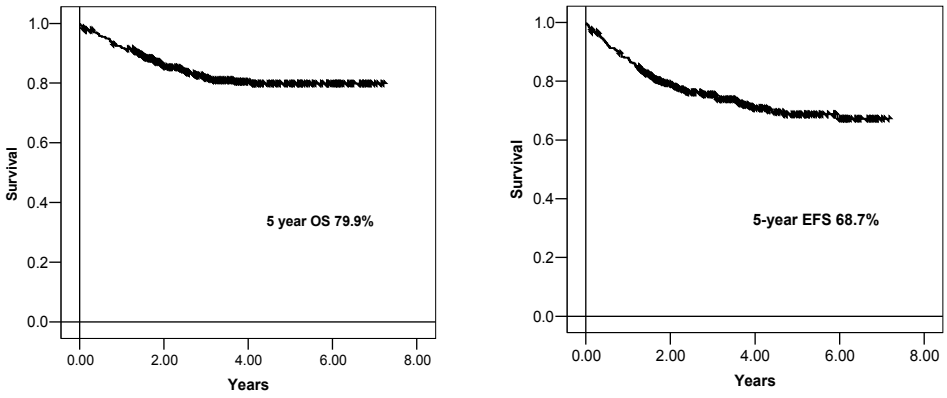


Figure 1: Overall survival and event free survival for ALL patients

While all patients were stratified for early response to induction therapy as measured by a Day 14 bone marrow evaluation, and treatment was intensified for these patients, this intensification was not found to be sufficient as patients with a poor Day 14 response continued to do significantly worse. The 5-year OS and EFS for patients with >5% blasts in the bone marrow on Day 14 as compared to those with <5% blasts was 58.4% v. 83% (p=0.001) and 45.6% v. 71.8% (p=0.019), respectively.

During this era we had further intensified the protocols for patients diagnosed with T-cell ALL and with biphenotypic acute leukemia (BAL), by considering these patients as very high risk. This assumption proved to be valid, as, in spite of more poor early responses in these immunophenotypic groups (pre-B ALL 5.5%, T ALL 15.7%, BAL 25%), the outcome was similar to that of the precursor B ALL patients (Pre B v. T v. BAL OS 81% v. 74.5% v. 71.6% p>0.5; EFS 68.4% v. 69.2% v. 79.5% p>0.5; See Figure 2)

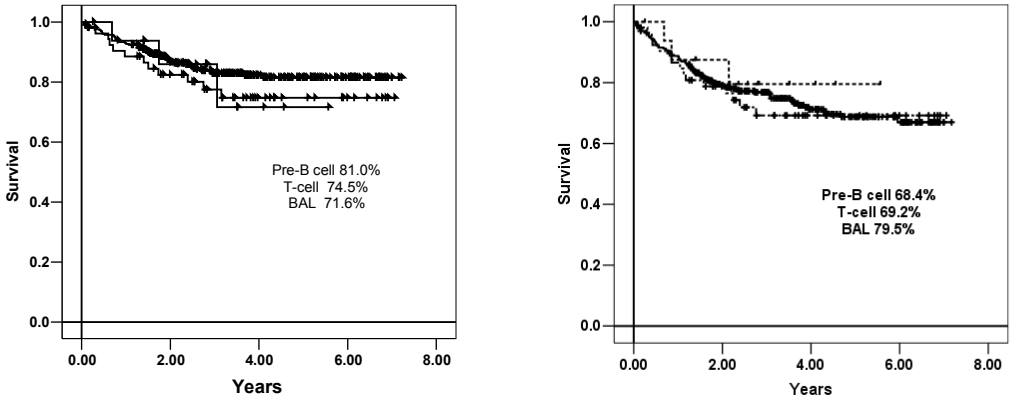


Figure 2: OS and EFS for patients according to immune phenotype.

CNS directed therapy has evolved during this period. We had limited prophylactic cranial radiation therapy to those patients who constituted the highest risk for CNS relapses; adolescents ≥10 years old and hyperleukocytosis ≥100K. These patients were treated according to the 1882 regimen A protocol which included 1800cGy cranial radiation therapy, while the remaining high risk pre-B ALL patients were treated with intensified intrathecal therapy without any radiation therapy (Regimen B). It has now been clearly shown, by our own results and that reported by the CCG, that there is no need to irradiate these CNS negative patients and intensified intrathecal therapy is sufficient.

Initially, based on the prevalent understanding we had opted to categorize patients with any involvement of the CSF with leukemia as CNS positive; thus patients with CNS 2 status were treated alongside CNS 3 patients. Subsequently, these CNS 2 patients were treated as high risk CNS negative patients. For CNS 2 patients the EFS and OS were the same whether they were treated with XRT or without (71.2% and 73.4%; $p>0.5$ and 71.6% v 91.3%; $p=0.37$, respectively). When we compared the CNS-2 patients who were treated without radiation therapy with the CNS-1 patients, there was no difference in the EFS or OS (CNS-1 v. CNS-2: EFS 71.6% v. 73.4% [$p>0.5$]; OS 86.9% v. 91.3% [$p>0.5$]). We have, however, continued to classify patients with CNS as high risk. These results confirmed that CNS 2 patients could be treated without radiation therapy.

Patients with CNS3 had a significantly worse OS and EFS (58.3% and 40.3%, respectively; $p\leq 0.001$ for both analyses) when compared to the other 2 categories. Ten of the 22 patients

with CNS3 disease suffered a relapse. The majority of the relapses (7/10) were in the bone marrow, while only two patients relapsed in the CNS. The final patient had a testicular relapse. Effective systemic therapy in addition to CNS directed therapy, therefore, is essential to maintain remission in patients with CNS positivity.

A total of 74/334 patients suffered a relapse. The sites of relapse are given in the Table below:

Site	n	%
BM	32	43.2
CNS	16	21.6
Testis	3	4.1
BM+CNS	17	23
BM+Testis	1	1.4
BM+CNS+Testis	2	2.7
CNS+Other	1	1.4
Other	2	2.7
	74	100

Sites of relapse for precursor B-cell ALL patients

The majority of the relapses (n=52; 70.3%) involved the bone marrow, either as an isolated site or in conjunction with another site. CNS involvement at relapse was found in 36 (48.6%) and testicular relapses occurred in 6 (14.3%; n= 42 boys). Most of the relapses seen in the precursor B-cell patient population occurred 'on therapy', with at least 75% of all relapses occurring in the first 2 years from diagnosis. This early timing for the relapses was seen in all the risk groups, with 50%, 75% and 100% relapses occurred within 2 years for the standard risk, high risk and poor risk patients, respectively.

The patterns of relapse would therefore suggest the need for early intensification of systemic therapy, certainly during the first year and probably during the first six months of therapy.

Keeping these results in mind, and after review of the results of the studies from various international ALL study groups we have formulated our new treatment strategy. This strategy utilizes standard approaches to the treatment of ALL that have been tested by international study groups and the results have been reported. In particular, due to our experience with the CCG 1800 series of protocols, the protocols follow the methodology set forth in the CCG 1900 series of protocols. Based on the results of these protocols we have utilized specific arms of therapy where they were found to be most efficacious when the results were published. The salient features of this strategy include the following:

- Earlier systemic intensification utilizing sustained duration of L-asparaginase use, and escalating dose IV methotrexate according to the Capizzi I strategy.
- Continuation of use of intensified intrathecal therapy for all patients without CNS 3 disease status.
- Utilization of Dexamethasone as the steroid formulation of choice for patients where the risk of toxicity related to Dexamethasone is not high. This would include patients receiving induction chemotherapy. All patients will get Prednisone during the induction chemotherapy, and will follow that with Dexamethasone during post induction treatment phases. Also, due to the high risk of osteonecrosis in patients older than 10 years of age, these patients will be preferentially treated with Prednisone rather than Dexamethasone in all phases of therapy other than Delayed Intensification (Re-induction). Dexamethasone during this phase for all patients will be given in a discontinuous fashion in order to minimize its related toxicity.
- Steroid associated toxicity will be assessed during induction for all patients, particularly those not receiving Anthracyclines. These results will be evaluated after a 6 month period. If steroid related toxicity is low for these patients receiving three-drug inductions consideration may be given to changing the steroid to Dexamethasone.
- Patients with a good early response to therapy, and those with out any adverse cytogenetic features, will continue to receive a single delayed intensification. A second delayed intensification phase will be administered to patients who exhibit a poor early response and to those with poor risk cytogenetics.
- Patients with T-ALL will be treated according to the same protocol, except that instead of receiving escalating dose methotrexate (Capizzi I), they will receive high dose methotrexate (5 gm/m^2) during the interim maintenance phase of therapy.
- Due to their particular biology and treatment requirements, patients with ALL in infancy and those with Biphenotypic Acute Leukemia will not be treated on these protocols. Please refer to the specific recommendations for these diagnoses in a different protocol.

2.0 Diagnostic Workup

The following studies need to be conducted on all patients prior to completion of diagnostic workup and initiation of therapy:

- Detailed history including past medical history, family history and immunization history
- Physical examination
- Complete Blood Count with differential
- The highest white blood count (WBC) for the patient recorded prior to initiation of chemotherapy will be used to determine the risk stratification. If the patient has a higher WBC count recorded at a major hospital prior to presentation at our institution, then that will be used to determine risk stratification. This WBC count needs to be documented in the patient medical records clearly.
- Serum electrolytes and renal function studies including creatnine and blood urea nitrogen (BUN)
- Hepatic function studies including total and direct bilirubin, alanine aminotranferase (ALT) and albumin.
- Serum calcium, magnesium, phosphate
- Serum uric acid
- Serum lactate dehydrogenase (LDH)
- Quantitative glucose 6 phosphate dehydrogenase (G6PD) levels
- Varicella IgG
- PT/PTT
- Chest x-ray
- Ultrasound abdomen
- Echocardiogram
- Bone marrow aspirate and biopsy
    - All patients with a suspicion of acute leukemia should have bone marrow aspiration and trephine biopsy. Peripheral blood sample may be used for diagnosis in certain special circumstances, e.g. dry tap or clinically unstable patient with peripheral absolute blast count >500 X 10^9/L.
    - In case of a dry tap or diluted aspirate, a second trephine biopsy should be done and preserved fresh in normal saline. This sample will be sent to the Flowcytometry Laboratory where it will be processed. After flowcytometric analysis the remaining pellet of cells can be used for Molecular- and Cytogenetic analysis.
- Cytogenetic studies
    - Bone marrow samples should be submitted for cytogenetic studies in preference over peripheral blood. Only when an adequate sample is not available from the aspirate will peripheral blood be used for cytogenetic studies. The following cytogenetic studies will be performed for all ALL samples:

        ➢ Routine cytogenetics for leukemic blasts

- FISH studies for *TEL-AML1*[t(12;21)], *BCR-ABL* [t(9;22)], *MLL* gene rearrangement, and chromosomes 4, 10 and 17 for trisomies.

- Boys with clinically evident testicular enlargement should have an ultrasound examination of the testes and testicular biopsy. The biopsy could be conducted by fine needle aspiration.
- Diagnostic cerebrospinal fluid (CSF) examination will not be conducted. The CSF examination will be delayed until the administration of the first intrathecal therapy. This examination should be done under conscious or procedural sedation in order to ensure the patient's immobility and should be done by a senior member of the team (i.e. should not be done by residents or by first year fellows during their initial six months of training).

3.0 Risk stratification

3.1 Risk Stratification for Pre- B ALL

3.1.1 Low risk

Patients should have all of the following features:

Age >1 year and <10 years
WBC count <50K
CNS negative (CNS1)
No testicular disease
DNA index 1.16-1.6
OR
Triple trisomy (trisomy of chromosomes 4, 10 and 17)
OR
TEL-AML1 fusion [t(12;21)]
No adverse cytogenetics
All these patients should have Day 14 <5% blasts

3.1.2 High risk

Patients with any one of the following would be considered HR:

Age ≥ 10 years
WBC count ≥ 50K
DNA index outside the LR range (except for patients with DNA index <0.8)
CNS 2 status
Testicular disease
E2A-PBX1 fusion or t(1;19)
All these patients should have Day 14 <5% blasts

3.1.3 Very high risk

CNS disease (CNS 3)
DNA index <0.8
Non infants with *MLL* gene rearrangement
All patients were on PALL 08-LR or PALL 08-HR protocols with Day 14 >5% blast

3.2 Risk Stratification for T-cell ALL

3.2.1 Low risk

WBC count <50K
CNS negative

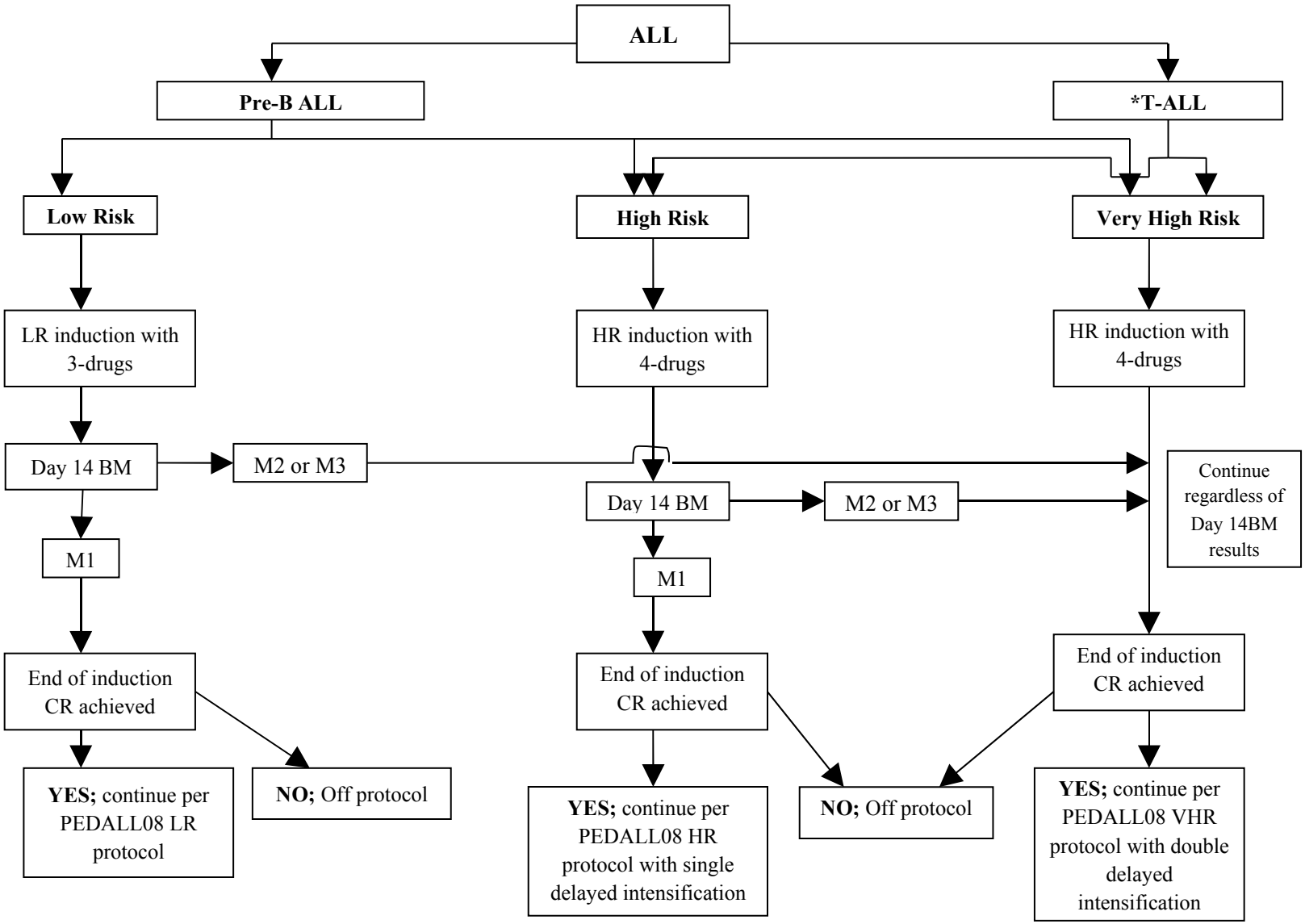
3.2.2 High risk

WBC count >50K
CNS positive

Infants with ALL, patients with Philadelphia Chromosome positive (PH+) ALL and patients with biphenotypic acute leukemia will NOT be treated according to this protocol. Please refer to specific protocols for these leukemia subtypes.

3.3 Algorithm for treatment assignment according to risk stratification (See next page).

Algorithm for treatment assignment



(Patients with T-ALL will receive HDMTX during interim maintenance I (Phase III) instead of escalating dose MTX (Capizzi I *

4.0 Definitions

4.1 Grading of CNS Leukemia:

- **CNS 1:** Cerebrospinal fluid (CSF) containing no leukemic blast cells as determined by morphologic assessment.
- **CNS 2:** CSF containing less than 5 white blood cells (WBC) per microliter (µl), with unequivocal leukemic blast cells determined by morphologic assessment.
- **CNS 3:** CSF containing 5 or greater than 5 WBC/µl, with unequivocal leukemic blast cells determined by morphologic assessment.

4.1 CSF Contamination by Peripheral Blood

- Traumatic Lumbar Puncture (TLP) occurs when there are equal to or greater than 10 red blood cells (RBC)/µl in the CSF.
- TLP+ occurs when there is a traumatic lumbar puncture with unequivocal leukemic blast cells determined by morphologic assessment.

4.3 Procedural guidelines to minimize traumatic lumbar punctures

- In order to minimize the incidence of traumatic lumbar punctures, an experienced member of the team should do all first Lumbar Puncture (LP).
- The first LP should be delayed until the diagnosis of the ALL is complete and should be conducted at the time of instillation of the first IT therapy.
- The first LP should be done under conscious sedation or short acting general anesthesia to minimize movement of the patient.

4.4 CNS status assignment for patients with traumatic lumbar punctures

- Patients with traumatic LP (≥ 10 RBC/µl) without any leukemic blasts in the CSF should be treated as negative for CNS leukemia.
- Patients with traumatic LP (≥ 10 RBC/HPF) and morphologically evident leukemic blasts (TLP+) should be categorized according to the CSF WBC count. Those with WBC ≥ 5/HPF should be treated as positive for CNS leukemia (CNS 3) and treated accordingly. While those with WBC <5/HPF should be treated as high risk but CNS disease negative (CNS 2).

5.0 Guidelines for Early Bone Marrow Response Assessment

All patients should undergo evaluation of the bone marrow on Day 14 of induction chemotherapy to assess early response to therapy. Bone marrow evaluation will include a bone marrow aspiration and a trephine biopsy. The bone marrow procedure should be conducted under procedural sedation in order to minimize patient trauma and to facilitate the collection of an adequate and representative sample.

Patients who have had delays in administration of induction chemotherapy due to toxicity should have the bone marrow evaluation done after completion of the second week of therapy, even if the time from the start of induction is longer than 2 weeks. This will enable response assessment following a uniform amount of anti-leukemia therapy for all patients.

It is anticipated that many patients will have bone marrow hypocellularity at this time point. Therefore dilute or hypocellular aspirate specimens will be encountered. In such situations, evaluation of the trephine biopsy becomes critical for adequate assessment of the marrow response, and thus a representative biopsy sample has to be collected.

The following points have to be considered when reporting Day 14 bone marrow studies:

- Adequacy of the sample, particularly the trephine biopsy sample, has to be evaluated and in case of a non-representative/inadequate sample the treating physician should be informed as early as possible, and no later than 3 days following the initial procedure.
- The bone marrow pathology report must indicate the estimated cellularity of the bone marrow as evaluated by the trephine biopsy specimen.
- Flow cytometry should be done on those samples which have ≥ 5% blasts by morphology.
- No cytogenetic or molecular studies need to be conducted on this marrow specimen.

The following actions should be taken according to the results of the Day 14 bone marrow:

- Representative marrow aspirate OR trephine biopsy sample with <5% blasts – Patient should be considered as a Rapid Early Responder (RER) and will continue on therapy according to his/her current protocol.
- Representative marrow aspirate OR trephine biopsy sample with ≥5% blasts – Patient should be considered as a Slow Early Responder (SER) and will receive subsequent therapy according to the very high risk protocol (PEDALL08-VHR).
- Non-representative/inadequate marrow aspirate AND trephine biopsy sample with ≥5% blasts – Patient should be considered as a Slow Early Responder (SER) and will receive subsequent therapy according to the very high risk protocol (PEDALL08-VHR).
- Non-representative/inadequate marrow aspirate AND trephine biopsy sample with <5% blasts – Bone marrow aspirate and trephine biopsy should be repeated at Day 21 of induction therapy. Patients with persistent leukemic blasts (≥5%) will be up-graded as indicated above and those with <5% blasts will continue on their current protocol.

6.0 Guidelines for End of Induction Evaluation

All patients will be evaluated at the end of a 28-day induction for determination of complete remission (CR) achievement. While the bone marrow evaluation is of pivotal importance, complete assessment of the patient needs to be done in order to determine remission status.

Remission will be achieved when the bone marrow reveals <5% leukemic blasts AND there is resolution of other sites of leukemic involvement, including organomegaly, lymphnodal enlargement, mediastinal widening, CNS positivity and testicular swelling. Also, there should be recovery of the peripheral blood counts. The following evaluations must be conducted, in addition to the bone marrow studies, in order to complete the workup for remission achievement:

- Physical examination should document complete normalization of prior organomegaly and lymphadenopathy.
- Complete blood count should document recovering cell counts and the CSF evaluation should be free of leukemic blasts.
- Chest X-ray should be done for all patients who had mediastinal widening at presentation to confirm its resolution.
- Boys with initial testicular disease who have persistence of testicular enlargement on physical examination should have a repeat biopsy to evaluate complete resolution of leukemic involvement.

All patients must have bone marrow aspiration and trephine biopsy at the end of the 28-day induction. For the majority of patients this should reveal marrow recovery with adequate cellular elements. The following points have to be considered when reporting Day 28 bone marrow studies:

- Adequacy of the sample has to be evaluated and in case of a non-representative/inadequate sample the treating physician should be informed as early as possible, and no later than 3 days following the initial procedure.
- Patients with ≥ 5% blasts by morphology should have flowcytometric evaluation done to determine the immune phenotype of the blast population.
- Minimal residual disease (MRD) evaluation by flow cytometry should be conducted for all patients. This result will not be used for risk stratification and treatment assignment at this time point, but will be evaluated for future use.
- Cytogenetic studies should be done for all patients who had a positive marker at diagnosis and for those patients who had unsuccessful karyotyping at the initial evaluation.
- Specific molecular and/or FISH studies should be done only for those cytogenetic markers that were positive at initial evaluation.

Low Risk Pre B-ALL Protocol

(PALL08-LR/CCG 1991 Arm IS)

Patients will be treated on this protocol only if they fulfill the criteria for Low Risk status as outlined in the section on Risk Stratification. (Section 3.0)

7.0 Low risk Pre-B ALL Protocol (PALL08-LR)

7.1 Treatment Plan

The first 14 days of chemotherapy will be identical for all patients on this protocol, with three induction agents. Patients with unfavorable marrow status at Day 14 will be switched to the PALL08-VHR Protocol by Day 21 or at the beginning of Consolidation. For definitions of Day 14 marrow response, please see Section 5.0 (Guidelines for Early Bone Marrow Response Assessment).

Patients who achieve a favorable marrow response at Day 14 will continue on the same induction protocol to complete 28 days of induction therapy. Patients who achieve a complete remission (CR) at the end of induction will continue on this protocol, receiving one month of Consolidation, two months of Interim maintenance, a single Delayed Intensification followed by Maintenance chemotherapy.

Patients who fail to achieve CR at the end of a 28-day induction will be considered induction failures, will be taken off this protocol and should receive second line induction therapy.

7.2 INDUCTION THERAPY (PHASE I) (DAYS 0 – 28)

All patients entered on the protocol will receive the same Induction chemotherapy from Days 0 – 28. Begin chemotherapy after overnight IV hydration, alkalinization and allopurinol or rasburicase therapy. Therapy should not be instituted until marrow samples for diagnostic and special studies have been obtained. During Induction, no medication dose will be reduced or delayed solely because of myelosuppression.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0
See Section 14.0 for Supportive Care Guidelines during Induction.

7.2.1 Prednisone

40 mg/m² PO q day divided TID, for 28 days from **Day 0-27**, adjusted upward to the nearest 2.5 mg as necessary for tablet size. (Use of liquid prednisone is acceptable; IV methylprednisolone may be used temporarily if needed, at a dose of 32 mg/m²/day.) Taper over 10 days (20 mg/m²/d x 2 days, 10 mg/m²/d x 3days, 5 mg/m²/d x 3 days, 2.5 mg/m²/d x 2 days).

7.2.2 Vincristine

1.5 mg/m² (2 mg maximum) IV push weekly on **Days 0, 7, 14, and 21**.

7.2.3 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 3 ± 1 day**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 9 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 3, 5, 7, 10, 12, 14, 17, 19, and 21**.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM x 9 doses may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

7.2.4 Intrathecal Cytosine Arabinoside (Ara-C)

Day 0

Age (yr)	1-1.99	2-2.99	≥ 3
Dose (mg)	30	50	70

The volume of CSF removed should be equal to the volume delivered.

7.2.5 IT Methotrexate

Days 14 and 28

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

The volume of CSF removed should be equal to the volume delivered

Day 14 Bone Marrow
If Day 14 marrow is M1, Patient should be considered as a Rapid Early Responder (RER) and will continue on therapy according to his/her current protocol.
If Day 14 marrow is M2 or M3 Patient should be considered as a Slow Early Responder (SER) and will receive subsequent therapy according to the very high risk protocol (PALL08-VHR). See section 5.0 for **Guidelines for Early Bone Marrow Response Assessment.**

Bone Marrow Day 28
If Day 28 marrow is M2/M3, patient is off protocol therapy and should receive alternate therapy. If Day 28 marrow is M1, patient will continue treatment per current protocol (PALL08-LR). See section 6.0 for **Guidelines for End of Induction Evaluation.**

7.3 CONSOLIDATION (PHASE II) (4 WEEKS)

Initiation of Therapy

Patients must have M1 marrow status at Day 28 to begin Consolidation therapy. Patients with M2/M3 marrow status at Day 28 are off protocol therapy.
Consolidation therapy will begin on Day 28 of Induction therapy provided that ANC is ≥ 1,000/μL and platelet count is ≥ 100,000/μL. If bone marrow aspirate results are not available or ANC and platelet counts have not recovered by Day 28, delay initiation of consolidation until the results are available and counts are adequate. All attempts should be made to limit delay in initiating consolidation therapy to less than 7 days.
Therapy interruptions should be made-up in all phases except during maintenance. In case of prolonged delays of 3 weeks or longer, please call the primary consultant and the protocol coordinator.

Therapy should be interrupted temporarily for presumed or proven serious infection.
See dose modifications due to toxicities (Section 12.0).

7.3.1 Vincristine
1.5 mg/m² IV push (2.0 mg maximum single dose) on **Day 0**.

7.3.2 Mercaptopurine
75 mg/m²/day PO on **Days 0-27**; drug should be given at least 1 hour before or 2 hours after the evening meal and should be taken without milk products.
Adjust dose of mercaptopurine using half-tablets and different doses to attain a weekly cumulative dose as close to 525mg/m^2 as possible.

See table below for tablet dosing guideline.

BSA (m^2)	Daily dose per week (1 tab = 50 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.4 - 0.44	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
0.45 - 0.5	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
0.51 - 0.55	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.56 - 0.6	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.61 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / d x 7	350 mg/wk
0.7 - 0.74	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.75 - 0.78	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
0.79 - 0.82	1 ½ tab / d x 3; 1 tab / d x 4	425 mg/wk
0.83 - 0.87	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.88 – 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 – 0.97	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
0.98 - 1.02	1 ½ tab / d x 7	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.12	2 tab / d x 2; 1½ tab / d x 5	575 mg/wk
1.13 - 1.16	2 tab / d x 3; 1½ tab / d x 4	600 mg/wk
1.17 - 1.2	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.21 - 1.25	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.26 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / d x 7	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2½ tab / d x 2; 2 tab / d x 5	750 mg/wk
1.46 - 1.50	2½ tab / d x 3; 2 tab / d x 4	775 mg/wk
1.51 - 1.55	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.56 - 1.59	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
1.60 - 1.64	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
1.65 - 1.69	2½ tab / d x 7	875 mg/wk
1.70 – 1.74	2 ½ tab /d x 6; 3 tab /d x 1	900 mg/wk
1.75- 1.78	2 ½ tab /d x 5; 3 tab /d x 2	925 mg/wk
1.79- 1.83	2 ½ tab /d x 4; 3 tab /d x 3	950 mg/wk
1.84- 1.88	2 ½ tab /d x 3; 3 tab /d x 4	975 mg/wk
1.89- 1.92	2 ½ tab /d x 2; 3 tab /d x 5	1000 mg/wk
1.93- 1.97	2 ½ tab /d x 1; 3 tab /d x 6	1025 mg/wk
1.98- 2.01	3 tab /d x 7	1050 mg/wk

Do not increase dose of mercaptopurine for ANC > 1500/μL until the Maintenance phase.

7.3.3 IT Methotrexate

Days 7, 14, and 21

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

The volume of CSF removed should be equal to the volume delivered

7.4 INTERIM MAINTENANCE (CAPIZZI I) (8 WEEKS) (PHASE III)

For all patients in remission upon completion of Phase II, Day 0 of Phase III will be Day 28 of Phase II or when peripheral counts recover with ANC > 1000/µL and platelet count > 100,000/µL. **During Phase III, all therapy should be interrupted for serious infection such as Varicella or *Pneumocystis carinii* pneumonia**.
Only methotrexate should be held for ANC < 750/µL or platelets < 75,000/µL. Methotrexate should be reinstituted on the first due date following the held dose; dosage should be decreased 20% from the previously administered dose. Missed doses are not made up. If counts do not recover within 21 days from a methotrexate dose, bone marrow aspiration should be performed, and, if not M3, repeat at 11 day intervals until count recovery or M3. Day 43 of Phase III will be the last day of chemotherapy administration during this phase, *regardless of the number of methotrexate doses given.*

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0.

7.4.1 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push x 5 administered on **Days 0, 10, 20, 30 and 40**.

7.4.2 Methotrexate

100 mg/m² IVPB IN D_5W 50ml (over 10 to 15 minutes) as initial dose on **day 0**. Escalate each subsequent dose by 50 mg/m²/dose from previous dose to toxicity (See Section 12.8 for guidelines). A maximum of 5 doses will be administered on Days 0, 10, 20, 30 and 40. The day of methotrexate dose administered can be altered ±1 day in order for it to be given on a weekday.

7.4.3 IT Methotrexate

Days 0, 30

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

The volume of CSF removed should be equal to the volume delivered.

7.5 DELAYED INTENSIFICATION (8 WEEKS) (PHASE IV)

This phase consists of reinduction and reconsolidation therapies. For all patients in remission upon completion of Phase III, Day 0 of Phase IV is Day 56 of Phase III or when the ANC is > 1000/µL and the platelet count > 100,000/µL, whichever occurs last**. Once begun, the reinduction and reconsolidation therapies are not interrupted for myelosuppression**

alone. Reconsolidation therapy is scheduled to begin on Day 28, but should be delayed until the ANC is > 1000/μL and platelets >100,000/μL. **Any serious infection (Varicella, *Pneumocystis carinii* pneumonia) or neutropenia, fever and proven infection warrants chemotherapy interruption at any time during phase IV.** Bone marrows are often difficult to interpret during this phase. Pancytopenia is inevitable and M2 recovery marrows are not uncommon.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0

7.5.1 Reinduction (4 weeks)

7.5.1.1 Vincristine

1.5 mg/m² (2.0 mg maximum dose) IV push weekly x 3 on **Days 0, 7 and 14**.

7.5.1.2 Doxorubicin

25 mg/m² IVPB IN D_5W 50ml (over 15 to 30 mins) through IV infusion weekly x 3 on **Days 0, 7, 14**.

7.5.1.3 Dexamethasone

10 mg/m²/day PO, **Days 0-6, 14-20** (14 days total: 7 days on, 7 days off, 7 days on). No taper. Divide into two daily doses, adjusting dose upward to nearest 0.25 mg, in order to comply with tablet size. Intravenous preparation (10 mg/m^2/day) may be used temporarily as needed.

7.5.1.4 IT Methotrexate

Day 0

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

The volume of CSF removed should be equal to the volume delivered.

7.5.1.5 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 3 ± 1 day**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 3, 5, 7, 10, 12 and 14**.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM x 6 doses may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

7.5.2 Reconsolidation (4 weeks)

Reconsolidation therapy is scheduled to begin on Day 28, but should be delayed until the ANC is > 1000/μL and platelets >100,000/μL.

7.5.2.1 Cyclophosphamide

1000 mg/m² IV in D_5W 50ml over 30 minutes on **Day 28**.
Reduce urine specific gravity to ≤ 1.015 with IV fluids before each dose. Maintain fluids at twice maintenance for at least 4 hours after each dose.
Use Lasix 0.25-0.5 mg/kg IV for urine output < 3 mL/kg/hr after cyclophosphamide.

7.5.2.2 Mesna

500 mg/m² IV should be administered in D_5W 50ml over 15-30 minutes prior to the cyclophosphamide dose and 3 hours post cyclophosphamide infusion.

7.5.2.3 Thioguanine

60 mg/m²/day PO x 14 days, to be administered at least 1 hr before or 2 hours after evening meal, on **Days 28-41** and it should be taken without milk products. Adjust dose of TG using half-tablet and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 420 mg/m² as possible.

BSA (m^2)	Daily dose per week (1 tab = 40 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.4 - 0.44	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.45 - 0.49	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.5 - 0.54	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.6 - 0.64	1 tab/ d x 6; ½ tab / d x 1	260 mg/wk
0.65 - 0.69	1 tab / day	280 mg/wk
0.70 - 0.74	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
0.75 - 0.79	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
0.8 - 0.84	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
0.85 - 0.89	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
0.9 - 0.94	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
0.95 – 0.99	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
1.0 - 1.04	1½ tab /day	420 mg/wk
1.05 - 1.09	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.10 - 1.14	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.15 - 1.19	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.2 - 1.24	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.25 - 1.29	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.3 - 1.34	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.35 - 1.39	2 tab / day	560 mg/wk
1.4 - 1.44	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
1.45 - 1.49	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk

1.5 - 1.54	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
1.55 - 1.59	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
1.60 - 1.64	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
1.65 - 1.69	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
1.7 - 1.74	2½ tab / d	700 mg/wk
1.75 - 1.79	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
1.8 – 1.84	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
1.85 – 1.89	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
1.9- 1.94	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
1.95- 1.99	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
2.0- 2.04	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk

7.5.2.4 Cytosine Arabinoside (Ara-C)

75 mg/m² IV push or SC x 8 days on **Days 29-32 and 36-39**.

7.5.2.5 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push weekly x 2 on **Days 42 and 49**.

7.5.2.6 Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 42**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 42, 45, 49, 52, 55 and 57.**

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

7.5.2.7 IT Methotrexate

Days 28 and 35

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

The volume of CSF removed should be equal the volume delivered.

7.6 MAINTENANCE - (PHASE V) (12 WEEKS PER COURSE)

7.6.1 Duration

Maintenance begins when the patient has recovered from Delayed Intensification with recovery of peripheral counts with ANC > 1000/µL and platelets > 100,000/µL. Therapy interruptions will not be made-up. In case of prolonged delays of 3 weeks or longer, please consult the primary consultant and the protocol coordinator.

The duration of Maintenance will be 2 calendar years for girls and 3 years for boys as measured from the time the patient started Interim Maintenance. The course in progress is stopped when the end therapy date is reached and that course is not completed.

7.6.2 Bone Marrow Aspirations

Routine bone marrow aspirates will not be obtained. ***Bone marrow aspirate should be performed if the patient has***:

1. circulating blast cells
2. unexplained organomegaly or lymphadenopathy
3. unexplained bone pain
4. documented or suspected extramedullary leukemia
5. Continued ANC < 750/µL or platelets < 75,000/µL more than 2 weeks after stopping chemotherapy for low counts.

Patients are off therapy if they develop an M3 marrow or extramedullary disease at any time while receiving therapy.

7.6.3 Dose Adjustments

Only MP and MTX will be interrupted for myelosuppression (see Section 12.9). The omitted doses will not be made up. The oral doses of MP and MTX should be adjusted to maintain ANC between 750/µL and 1500/µL and platelets ≥ 75,000/µL.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0

7.6.4 Maintenance Chemotherapy

7.6.4.1 IT Methotrexate

Day 0 for all courses**.**

.

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

The volume of CSF removed should be equal to the volume delivered.

7.6.4.2 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push x 3 on **Days 0, 28, 56**.

7.6.4.3 Dexamethasone

6 mg/m² PO divided TID x 5 days every 28 days on **Days 0-4, 28-32, 56-60**. Patients over 10 years of age should not receive Dexamethasone and should instead receive Prednisone (40 mg/m²/day). Patients who are initially less than 10 years of age should be changed to Prednisone following their 10th birthday.

7.6.4.4 Mercaptopurine (MP)

75 mg/m²/day PO daily to be administered at least 1 hr before or 2 hours after evening meal on **Days 0-83** and it should be taken without milk products. Adjust dose of MP using half-

tablet and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 525 mg/m² as possible. Dose adjustment may be necessary for patients with severe renal impairment.

BSA (m^2)	Daily dose per week (1 tab = 50 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.4 - 0.44	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
0.45 - 0.5	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
0.51 - 0.55	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.56 - 0.6	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.61 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / d x 7	350 mg/wk
0.7 - 0.74	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.75 - 0.78	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
0.79 - 0.82	1 ½ tab / d x 3; 1 tab / d x 4	425 mg/wk
0.83 - 0.87	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.88 – 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 – 0.97	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
0.98 - 1.02	1 ½ tab / d x 7	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.12	2 tab / d x 2; 1½ tab / d x 5	575 mg/wk
1.13 - 1.16	2 tab / d x 3; 1½ tab / d x 4	600 mg/wk
1.17 - 1.2	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.21 - 1.25	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.26 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / d x 7	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2½ tab / d x 2; 2 tab / d x 5	750 mg/wk
1.46 - 1.50	2½ tab / d x 3; 2 tab / d x 4	775 mg/wk
1.51 - 1.55	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.56 - 1.59	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
1.60 - 1.64	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
1.65 - 1.69	2½ tab / d x 7	875 mg/wk
1.70 – 1.74	2 ½ tab /d x 6; 3 tab /d x 1	900 mg/wk
1.75- 1.78	2 ½ tab /d x 5; 3 tab /d x 2	925 mg/wk
1.79- 1.83	2 ½ tab /d x 4; 3 tab /d x 3	950 mg/wk
1.84- 1.88	2 ½ tab /d x 3; 3 tab /d x 4	975 mg/wk
1.89- 1.92	2 ½ tab /d x 2; 3 tab /d x 5	1000 mg/wk
1.93- 1.97	2 ½ tab /d x 1; 3 tab /d x 6	1025 mg/wk
1.98- 2.01	3 tab /d x 7	1050 mg/wk

7.6.4.5 Methotrexate

20 mg/m²/dose PO weekly (escalate as per Section 12.9) to be administered on **Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77.**

7.7 End of Therapy

Therapy will end for patients as follows:
1) Girls will end therapy 2 years from the beginning of Interim Maintenance.
2) Boys will end therapy 3 years from the beginning of Interim Maintenance.
3) Therapy will end at the anniversary date and the course in progress will **NOT** be completed.

High Risk Pre B-ALL Protocol (PALL08-HR/CCG 1961 Arm C)

Patients will be treated on this protocol only if they fulfill the criteria for High Risk status as outlined in the section on Risk Stratification. (Section 3.0)

8.0 High risk Pre-B ALL Protocol (PALL08-HR)

8.1 Treatment Plan

The first 14 days of chemotherapy will be identical for all patients on this protocol, with four induction agents. Patients with unfavorable marrow status at Day 14 will be switched to the PALL08-VHR Protocol by Day 21 or at the beginning of Consolidation. For definitions of Day 14 marrow response, please see Section 5.0 (Guidelines for Early Bone Marrow Response Assessment).

Patients who achieve a favorable marrow response at Day 14 will continue on the same induction protocol to complete 28 days of induction therapy. Patients who achieve a complete remission (CR) at the end of induction will continue on this protocol, receiving 8 weeks of Consolidation, 9 weeks of Interim Maintenance, and single Delayed Intensification followed by Maintenance chemotherapy.

8.2 INDUCTION THERAPY (PHASE I) (DAYS 0 – 28)

All patients entered on study will receive the same Induction chemotherapy from Days 0 - 28 Begin chemotherapy after overnight IV hydration, alkalinization and allopurinol or rasburicase therapy. Therapy should not be instituted until marrow samples for diagnostic and special studies have been obtained. During Induction, no medication dose will be reduced or delayed solely because of myelosuppression. A baseline echocardiogram or radionuclide ejection fraction should precede anthracycline therapy.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0
See Section 14.0 for Supportive Care Guidelines during Induction.

8.2.1 Prednisone

60 mg/m² PO q day divided TID, for 28 days from **Day 0-27**, adjusted upward to the nearest 2.5 mg as necessary for tablet size. (Use of liquid prednisone is acceptable; IV methylprednisolone may be used temporarily if needed, at a dose of 48 mg/m²/day.) Taper over 10 days (30 mg/m²/d x 2 days, 15 mg/m²/d x 3days, 7.5 mg/m²/d x 3 days, 3.75 mg/m²/d x 2 days).

8.2.2 Vincristine

1.5 mg/m² (2 mg maximum) IV push weekly on **Days 0, 7, 14, and 21**.

8.2.3 Daunomycin

25 mg/m² IVPB in D5W 50ml (over 15 to 30 mins) weekly on Days **0, 7, 14, and 21**.

8.2.4 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 3 ± 1 day**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 9 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 3, 5, 7, 10, 12, 14, 17, 19, and 21**.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM x 9 doses may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

8.2.5 Intrathecal Cytosine Arabinoside (Ara-C)

Day 0

Age (yr)	1-1.99	2-2.99	≥ 3
Dose (mg)	30	50	70

The volume of CSF removed should equal at least half the volume delivered.

8.2.6 IT Methotrexate
Days 14 and 28

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

The volume of CSF removed should be equal to the volume delivered

8.Day 14 Bone Marrow
If Day 14 marrow is M1, Patient should be considered as a Rapid Early Responder (RER) and will continue on therapy according to his/her current protocol.
If Day 14 marrow is M2 or M3 patient should be considered as a Slow Early Responder (SER) and will receive subsequent therapy according to the very high risk protocol (PALL08-VHR). See section 5.0 for **Guidelines for Early Bone Marrow Response Assessment.**

Bone Marrow Day 28
If Day 28 marrow is M2/M3, patient is off protocol therapy and should receive alternate therapy. If Day 28 marrow is M1, patient will continue treatment per current protocol (PALL08-HR). See section 6.0 for **Guidelines for End of Induction Evaluation.**

8.3 CONSOLIDATION (9 WEEKS) (PHASE II)
For all patients M1 on Day 28 of Induction, Day 0 of Consolidation will be Day 35 of Induction or when peripheral counts recover with an absolute neutrophil count (ANC) > 750/ µL and a platelet count >75x 10^9/L. **Once Consolidation has begun it may be interrupted for myelosuppression (ANC < 750/µL or platelets < 75,000/µL) on Day 28 only**. **Once the Day 0 or Day 28 cyclophosphamide has been given, MP, Ara-C, Vincristine, asparaginase, IT methotrexate should not be interrupted solely for myelosuppression**. Therapy must be interrupted in patients who are **neutropenic, febrile and proven infected** and should be resumed when the signs of infection have abated.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0.

8.3.1 Prednisone
Continue prednisone taper as indicated in Induction.

8.3.2 Cyclophosphamide
1000 mg/m² IVPB (over 30 minutes) in D_5W50 ml x 2 doses on **Days 0 and 28**.
Reduce urine specific gravity to ≤1.015 with IV fluids before each dose.
Maintain fluids at twice maintenance for at least 4 hours after each dose.
Use Lasix 0.25-0.5 mg/kg IV for urine output < 3 ml/kg/hr after cyclophosphamide.

8.3.3 Mesna
500 mg/m² IVPB in D_5W 50ml should be administered 15-30 minutes prior to the cyclophosphamide dose and 3 hours post cyclophosphamide infusion on day 0 and 28.

8.3.4 Cytosine Arabinoside (Ara-C)

75 mg/m²/day IV push or SC x 16 doses **Days 1-4, 7-10, 29-32, and 35-38**.

8.3.5 Mercaptopurine

60 mg/m²/day PO, at least 1 hr before or 2 hours after evening meal on **Days 0-13 and 28-41**. Should be taken without milk products. Adjust dose of MP using half-tablets and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 420 mg/ m² as possible.

BSA (m^2)	Daily dose per week (1 tab = 50 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6	150 mg/wk
0.4 - 0.44	½ tab / d x 7	175 mg/wk
0.45 - 0.5	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.51 - 0.55	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
0.56 - 0.6	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
0.61 - 0.65	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.66 - 0.71	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.72 - 0.77	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.78 - 0.83	1 tab / d x 7	350 mg/wk
0.84 - 0.89	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.9 - 0.95	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
0.96 - 1.01	1½ tab / d x 3; 1 tab / d x 4	425 mg/wk
1.02 - 1.07	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.08 - 1.13	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.14 - 1.19	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.20 - 1.25	1½ tab / d x 7	525 mg/wk
1.26 - 1.30	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.31 - 1.36	2 tab / d x 2; 1½ tab / d x 5	575 mg/wk
1.37 - 1.43	2 tab / d x 3; 1½ tab / d x 4	600 mg/wk
1.44 - 1.49	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.50 - 1.55	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.56 - 1.61	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.62 - 1.67	2 tab / d x 7	700 mg/wk
1.68 - 1.73	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.74 - 1.79	2½ tab / d x 2; 2 tab / d x 5	750 mg/wk
1.80 - 1.85	2½ tab / d x 3; 2 tab / d x 4	775 mg/wk
1.86 - 1.91	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.92 - 1.97	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
1.98 - 2.03	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk

Do not increase dose for ANC > 1500/µL until maintenance therapy.

8.3.6 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push x 4 on **Days 14, 21, 42, 49**.

8.3.7 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 2 doses administered on **Days 14 and 42**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses each administered thrice weekly on a Sat-Mon-Wed schedule can be used beginning on **Days 14 and 42**.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM x 6 doses each may be substituted. Erwinia asparaginase should be administered on alternate days beginning on **Days 14 and 42,** without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

8.3.8 IT Methotrexate

Once a week x 4 on **Days 0, 7, 14, 21**

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

The volume of CSF removed should be equal to the volume delivered.

Contact Protocol Coordinator if patient receives a total of < 5 doses of IT chemotherapy during Induction and Consolidation.

8.4 INTERIM MAINTENANCE (CAPIZZI I) (8 WEEKS) (PHASE III)

For all patients in remission upon completion of Phase II, Day 0 of Phase III will be Day 63 of Phase II or when peripheral counts recover with ANC > 750/µL and platelet count > 75,000/µL. **During Phase III, all therapy should be interrupted for serious infection such as Varicella or *Pneumocystis carinii* pneumonia**.
Only methotrexate should be held for ANC < 750/µL or platelets < 75,000/µL. Methotrexate should be reinstituted on the first due date following the held dose; dosage should be decreased 20% from the previously administered dose. Missed doses are not made up. If counts do not recover within 21 days from a methotrexate dose, bone marrow aspiration should be performed, and, if not M3, repeat at 11 day intervals until count recovery or M3. Day 43 of Phase III will be the last day of chemotherapy administration during this phase, *regardless of the number of methotrexate doses given. Vincristine and Asparaginase is to be administered regardless of counts.*

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0.

8.4.1 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push x 5 administered on **Days 0, 10, 20, 30 and 40.**

8.4.2 Methotrexate

100 mg/m² IVPB IN D_5W 50ml (over 10 to 15 minutes) as initial dose on **day 0**. Escalate each subsequent dose by 50 mg/m²/dose from previous dose to toxicity (See Section 12.8 for

guidelines). A maximum of 5 doses will be administered on **Days 0, 10, 20, 30 and 40**. The day of methotrexate dose administered can be altered ±1 day in order for it to be given on a weekday.

8.4.3 Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 2 doses administered on **Days 1 and 21**.

If PEG asparaginase is not available, substitute native E. coli asparaginase 15,000 IU/m^2 IM x 1 the day after each dose of IV methotrexate is given.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs substitute Erwinia asparaginase 25,000 U/m^2 x 1 the day after each dose of IV methotrexate is given.

If IV methotrexate is held due to neutropenia or thrombocytopenia, the dose of E. coli or Erwinia asparaginase should ***not*** be withheld. It may be administered on the same day as vincristine is given.

See Section 12.1 for clarification of dose and schedule for substitutions.

8.4.4 IT Methotrexate

Days 0, 30

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

The volume of CSF removed should be equal to the volume delivered.

8.5 DELAYED INTENSIFICATION (8 WEEKS) (PHASE IV)

This phase consists of reinduction and reconsolidation therapies. For all patients in remission upon completion of Phase III, Day 0 of Phase IV is Day 56 of Phase III or when the ANC is > 750/μL and the platelet count > 75,000/μL, whichever occurs last**. Once begun, the reinduction and reconsolidation therapies are not interrupted for myelosuppression alone**. Reconsolidation therapy is scheduled to begin on Day 28, but should be delayed until the ANC is > 750/μL and platelets >75,000/μL. **Any serious infection (Varicella, *Pneumocystis carinii* pneumonia) or neutropenia, fever and proven infection warrants chemotherapy interruption at any time during phase IV.** Bone marrows are often difficult to interpret during this phase. Pancytopenia is inevitable and M2 recovery marrows are not uncommon.

All patients should have echocardiographic evaluation of cardiac function prior to initiation of Reinduction.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0.

8.5.1 Reinduction (4 weeks)

8.5.1.1 Vincristine

1.5 mg/m² (2.0 mg maximum dose) IV push weekly x 3 on **Days 0, 7 and 14**.

8.5.1.2 Doxorubicin

25 mg/m² IVPB (over 15 to 30 mins) through IV infusion in D_5W50 ml weekly x 3 on **Days 0, 7, 14.**

8.5.1.3 Dexamethasone

10 mg/m²/day PO x 14 days administered in two or three divided daily doses on **Days 0-6 and 14-20**. **No taper.**

8.5.1.4 IT Methotrexate

Day 0

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

The volume of CSF removed should be equal to the volume delivered.

8.5.1.5 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 3 ± 1 day**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 3, 5, 7, 10, 12 and 14.**

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

8.5.2 Reconsolidation (4 weeks)

8.5.2.1 Cyclophosphamide

1000 mg/m² IVPB in D_5W 50ml over 30 minutes on **Day 28**.
Reduce urine specific gravity to ≤ 1.015 with IV fluids before each dose. Maintain fluids at twice maintenance for at least 4 hours after each dose.
Use Lasix 0.25-0.5 mg/kg IV for urine output < 3 mL/kg/hr after cyclophosphamide.

8.5.2.2 Mesna

500 mg/m² IVPB in 50ml D_5W should be administered 15-30 minutes prior to the cyclophosphamide dose and 3 hours post cyclophosphamide infusion.

8.5.2.3 Thioguanine

60 mg/m²/day PO x 14 days, to be administered at least 1 hr before or 2 hours after evening meal, on **Days 28-41**. Should be taken without milk products. Adjust dose of TG using half-tablet and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 420 mg/m² as possible.

BSA (m^2)	Daily dose per week (1 tab = 40 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.4 - 0.44	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.45 - 0.49	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.5 - 0.54	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.6 - 0.64	1 tab/ d x 6; ½ tab / d x 1	260 mg/wk
0.65 - 0.69	1 tab / day	280 mg/wk
0.70 - 0.74	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
0.75 - 0.79	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
0.8 - 0.84	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
0.85 - 0.89	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
0.9 - 0.94	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
0.95 – 0.99	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
1.0 - 1.04	1½ tab /day	420 mg/wk
1.05 - 1.09	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.10 - 1.14	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.15 - 1.19	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.2 - 1.24	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.25 - 1.29	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.3 - 1.34	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.35 - 1.39	2 tab / day	560 mg/wk
1.4 - 1.44	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
1.45 - 1.49	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
1.5 - 1.54	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
1.55 - 1.59	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
1.60 - 1.64	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
1.65 - 1.69	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
1.7 - 1.74	2½ tab / d	700 mg/wk
1.75 - 1.79	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
1.8 – 1.84	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
1.85 – 1.89	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
1.9- 1.94	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
1.95- 1.99	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
2.0- 2.04	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk

Do not increase dose for ANC > 1500/µL until maintenance therapy.

8.5.2.4 Cytosine Arabinoside (Ara-C)

75 mg/m² IV push or SC x 8 days on **Days 29-32 and 35-38**.

8.5.2.5 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push weekly x 2 on **Days 42 and 49**.

8.5.2.6 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 42**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 42, 45, 49, 52, 55 and 57.**

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

8.5.2.7 IT Methotrexate

Days 28 and 35

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

The volume of CSF removed should be equal to at least half the volume delivered.

8.6 MAINTENANCE - (PHASE V) (12 WEEKS PER COURSE)

8.6.1 Duration

Maintenance begins when the patient has recovered from Delayed Intensification with recovery of peripheral counts with ANC > 750/µL and platelets > 75,000/µL.
The duration of Maintenance will be 2 calendar years for girls and 3 years for boys as measured from the time the patient started Interim Maintenance. The course in progress is stopped when the end therapy date is reached and that course is not completed.

8.6.2 Bone Marrow Aspirations

Routine bone marrow aspirates will not be obtained. ***Bone marrow aspirate should be performed if the patient has***:

6. circulating blast cells
7. unexplained organomegaly or lymphadenopathy
8. unexplained bone pain
9. documented or suspected extramedullary leukemia
10. Continued ANC < 750/µL or platelets < 75,000/µL more than 2 weeks after stopping chemotherapy for low counts.

Patients are off therapy if they develop an M3 marrow or extramedullary disease at any time while receiving therapy.

8.6.3 Dose Adjustments

Only MP and MTX will be interrupted for myelosuppression (see Section 12.9). The omitted doses will not be made up. The oral doses of MP and MTX should be adjusted to maintain ANC between 750/μL and 1500/μL and platelets ≥ 75,000/μL.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0

8.6.4 Maintenance Chemotherapy

8.6.4.1 IT Methotrexate

Day 0 and 28 **of courses 1-4.**
Day 0 for **courses 5 – completion.**

.

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

The volume of CSF removed should be equal to the volume delivered.

8.6.4.2 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push x 3 on **Days 0, 28, 56**.

8.6.4.3 Dexamethasone

6 mg/m² PO divided TID x 5 days every 28 days on **Days 0-4, 28-32, 56-60.** Patients over 10 years of age should not receive Dexamethasone and should instead receive Prednisone (40 mg/m²/day). Patients who are initially less than 10 years of age should be changed to Prednisone following their 10th birthday.

8.6.4.4 Mercaptopurine (MP)

75 mg/m²/day PO daily to be administered at least 1 hr before or 2 hours after evening meal on **Days 0-83**. Should be taken without milk products. Adjust dose of MP using half-tablet and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 525 mg/m² as possible.

BSA (m^2)	Daily dose per week (1 tab = 50 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.4 - 0.44	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
0.45 - 0.5	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
0.51 - 0.55	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.56 - 0.6	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.61 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / d x 7	350 mg/wk
0.7 - 0.74	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.75 - 0.78	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
0.79 - 0.82	1 ½ tab / d x 3; 1 tab / d x 4	425 mg/wk
0.83 - 0.87	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk

0.88 – 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 – 0.97	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
0.98 - 1.02	1 ½ tab / d x 7	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.12	2 tab / d x 2; 1½ tab / d x 5	575 mg/wk
1.13 - 1.16	2 tab / d x 3; 1½ tab / d x 4	600 mg/wk
1.17 - 1.2	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.21 - 1.25	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.26 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / d x 7	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2½ tab / d x 2; 2 tab / d x 5	750 mg/wk
1.46 - 1.50	2½ tab / d x 3; 2 tab / d x 4	775 mg/wk
1.51 - 1.55	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.56 - 1.59	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
1.60 - 1.64	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
1.65 - 1.69	2½ tab / d x 7	875 mg/wk
1.70 – 1.74	2 ½ tab /d x 6; 3 tab /d x 1	900 mg/wk
1.75- 1.78	2 ½ tab /d x 5; 3 tab /d x 2	925 mg/wk
1.79- 1.83	2 ½ tab /d x 4; 3 tab /d x 3	950 mg/wk
1.84- 1.88	2 ½ tab /d x 3; 3 tab /d x 4	975 mg/wk
1.89- 1.92	2 ½ tab /d x 2; 3 tab /d x 5	1000 mg/wk
1.93- 1.97	2 ½ tab /d x 1; 3 tab /d x 6	1025 mg/wk
1.98- 2.01	3 tab /d x 7	1050 mg/wk

8.6.4.5 Methotrexate

20 mg/m²/dose PO weekly (escalate as per Section 12.9) to be administered on **Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77**. Oral MTX is omitted on Day 28 for the first 4 courses of therapy due to the administration of Intrathecal MTX.

8.7 End of Therapy

Therapy will end for patients as follows:
1) Girls will end therapy 2 years from the beginning of Interim Maintenance (I).
2) Boys will end therapy 3 years from the beginning of Interim Maintenance (I).
3) Therapy will end at the anniversary date and the course in progress will **NOT** be completed.

Very High Risk Pre B-ALL Protocol (PALL08-VHR/CCG 1961 Arm D)

Patients will be treated on this protocol only if they fulfill the criteria for Very High Risk (VHR) status as outlined in the section on Risk Stratification. (Section 3.0)

9.0 Very High risk Pre-B ALL Protocol (PALL08-VHR)

9.1 Treatment Plan

The first 14 days of chemotherapy will be identical for all patients on this protocol, with four induction agents. Patients on either the LR or the HR protocol with unfavorable marrow status at Day 14 will be switched to the PALL08-VHR Protocol by Day 21 or at the beginning of Consolidation. For definitions of Day 14 marrow response, please see Section 5.0 (Guidelines for Early Bone Marrow Response Assessment).

Patients who are originally categorized as VHR will continue on the same induction protocol to complete 28 days of induction chemotherapy regardless of the Day 14 BM results. Patients who achieve a complete remission (CR) at the end of induction will continue on this protocol, receiving 8 weeks of Consolidation, two Interim maintenance phases 9 weeks each, and double Delayed Intensification followed by Maintenance chemotherapy.

Patients who fail to achieve CR at the end of a 28-day induction will be considered induction failures, will be taken off this protocol and should receive second line induction therapy.

All patients with CNS leukemia (CNS3 status, cranial nerve palsy or brain parenchymal infiltrates) will receive radiation therapy to the craniospinal field during the Consolidation phase of therapy. Patients who are CNS negative will receive cranial prophylactic radiation therapy during the Consolidation phase.

9.2 INDUCTION THERAPY (PHASE I) (DAYS 0 – 28)

All patients entered on study will receive the same Induction chemotherapy from Days 0 - 28 Begin chemotherapy after overnight IV hydration, alkalinization and allopurinol or rasburicase therapy. Therapy should not be instituted until marrow samples for diagnostic and special studies have been obtained. During Induction, no medication dose will be reduced or delayed solely because of myelosuppression. A baseline echocardiogram or radionuclide ejection fraction should precede anthracycline therapy.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0
See Section 14.0 for Supportive Care Guidelines during Induction.

9.2.1 Prednisone

60 mg/m² PO q day divided TID for 28 days, from **Day 0-27**, adjusted upward to the nearest 2.5 mg as necessary for tablet size. (Use of liquid prednisone is acceptable; IV methylprednisolone may be used temporarily if needed, at a dose of 48 mg/m²/day.) Taper over 10 days (30 mg/m²/d x 2 days, 15 mg/m²/d x 3days, 7.5 mg/m²/d x 3 days, 3.75 mg/m²/d x 2 days).

9.2.2 Vincristine

1.5 mg/m² (2 mg maximum) IV push weekly on **Days 0, 7, 14, and 21**.

9.2.3 Daunomycin

25 mg/m² IVPB (over 15 to 30 mins) in D_5W 50ml weekly on Days **0, 7, 14, and 21**.

9.2.4 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 3 $\pm$ 1 day**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 9 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 3, 5, 7, 10, 12, 14, 17, 19, and 21**.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM x 9 doses may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

9.2.5 Intrathecal Cytosine Arabinoside (Ara-C)

Day 0

Age (yr)	1-1.99	2-2.99	≥ 3
Dose (mg)	30	50	70

The volume of CSF removed should equal the volume delivered.

9.2.6 Intrathecal Methotrexate

Should be administered on **Days 14 and 28 for patients who are CNS 1/2**. Additional IT MTX should be administered on **Days 7 and 21 for patients who are CNS 3 or have other evidence of CNS leukemia.**

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

The volume of CSF removed should be equal to the volume delivered

Bone Marrow Day 14
If Day 14 marrow is M1, Patient should be considered as a Rapid Early Responder (RER), and if Day 14 marrow is M2 or M3 the patient should be considered as a Slow Early Responder (SER).
Patients will continue on the same induction protocol to complete 28 days of induction chemotherapy regardless of Day 14 BM results.

See section 5.0 for **Guidelines for Early Bone Marrow Response Assessment**

Bone Marrow Day 28
If Day 28 marrow is M2/M3, patient is off protocol therapy and should receive alternate therapy. If Day 28 marrow is M1, patient will continue treatment per current protocol (PALL08-VHR).
See section 6.0 for **Guidelines for End of Induction Evaluation**

9.3 CONSOLIDATION (9 WEEKS) (PHASE II)

For all patients M1 on Day 28 of Induction, Day 0 of Consolidation will be Day 35 of Induction or when peripheral counts recover with an absolute neutrophil count (ANC) > 750/ μL and a platelet count >75x 10^9/L. **Once Consolidation has begun it may be interrupted for myelosuppression (ANC < 750/μL or platelets < 75,000/μL) on Day 28 only**. **Once the Day 0 or Day 28 cyclophosphamide has been given, MP, Ara-C, Vincristine, asparaginase, IT methotrexate should not be interrupted solely for myelosuppression**. Therapy must be interrupted in patients who are **neutropenic, febrile and proven infected** and should be resumed when the signs of infection have abated.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0

9.3.1 Prednisone

Continue prednisone taper as indicated in Induction.

9.3.2 Cyclophosphamide

1000 mg/m² IVPB (over 30 minutes) in D5W 50ml x 2 doses on **Days 0 and 28**.
Reduce urine specific gravity to ≤1.015 with IV fluids before each dose.
Maintain fluids at twice maintenance for at least 4 hours after each dose.
Use Lasix 0.25-0.5 mg/kg IV for urine output < 3 ml/kg/hr after cyclophosphamide.

9.3.3 Mesna

500 mg/m² IVPB should be administered in D5W 50ml 15-30 minutes prior to the cyclophosphamide dose and 3 hours post cyclophosphamide infusion.

9.3.4 Cytosine Arabinoside (Ara-C)

75 mg/m²/day IV push or SC x 16 doses **Days 1-4, 7-10, 29-32, and 35-38**.

9.3.5 Mercaptopurine

60 mg/m²/day PO, at least 1 hr before or 2 hours after evening meal on Days **0-13 and 28-41.** Should be taken without milk products. Adjust dose of MP using half-tablets and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 420 mg/m² as possible.

BSA (m^2)	Daily dose per week (1 tab = 50 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6	150 mg/wk
0.4 - 0.44	½ tab / d x 7	175 mg/wk
0.45 - 0.5	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.51 - 0.55	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
0.56 - 0.6	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
0.61 - 0.65	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.66 - 0.71	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.72 - 0.77	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.78 - 0.83	1 tab / d x 7	350 mg/wk
0.84 - 0.89	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.9 - 0.95	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
0.96 - 1.01	1½ tab / d x 3; 1 tab / d x 4	425 mg/wk
1.02 - 1.07	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.08 - 1.13	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.14 - 1.19	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.20 - 1.25	1½ tab / d x 7	525 mg/wk
1.26 - 1.30	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.31 - 1.36	2 tab / d x 2; 1½ tab / d x 5	575 mg/wk
1.37 - 1.43	2 tab / d x 3; 1½ tab / d x 4	600 mg/wk
1.44 - 1.49	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.50 - 1.55	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.56 - 1.61	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.62 - 1.67	2 tab / d x 7	700 mg/wk
1.68 - 1.73	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.74 - 1.79	2½ tab / d x 2; 2 tab / d x 5	750 mg/wk
1.80 - 1.85	2½ tab / d x 3; 2 tab / d x 4	775 mg/wk
1.86 - 1.91	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.92 - 1.97	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
1.98 - 2.03	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk

Do not increase dose for ANC > 1500/µL until maintenance therapy.

9.3.6 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push x 4 on **Days 14, 21, 42, 49**.

9.3.7 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 2 doses administered on **Days 14 and 42**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses each administered thrice weekly on a Sat-Mon-Wed schedule can be used beginning on **Days 14 and 42**.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM x 6 doses each may be substituted. Erwinia asparaginase should be administered on alternate days beginning on **Days 14 and 42,** without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

9.3.8 Intrathecal Methotrexate

Once a week x 4 on **Days 0, 7, 14, 21.**

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

The volume of CSF removed should be equal to the volume delivered.

Contact primary consultant and protocol coordinator if patient receives a total of <5 doses of IT chemotherapy during Induction and Consolidation.

9.3.9 Radiation Therapy

Referral to Radiation Oncology should be done prior to Day 0 Consolidation, in order for the radiation therapy to be initiated and completed during the Consolidation phase of therapy. See Sections 14.13.

9.4 INTERIM MAINTENANCE I (CAPIZZI I) (8 WEEKS) (PHASE III)

For all patients in remission upon completion of Phase II, Day 0 of Phase III will be Day 63 of Phase II or when peripheral counts recover with ANC > 750/µL and platelet count > 75,000/µL. **During Phase III, all therapy should be interrupted for serious infection such as Varicella or *Pneumocystis carinii* pneumonia**.
Only methotrexate should be held for ANC < 750/µL or platelets < 75,000/µL. Methotrexate should be reinstituted on the first due date following the held dose; dosage should be decreased 20% from the previously administered dose. Missed doses are not made up. If counts do not recover within 21 days from a methotrexate dose, bone marrow aspiration should be performed, and, if not M3, repeat at 11 day intervals until count recovery or M3. Day 43 of Phase III will be the last day of chemotherapy administration during this phase, *regardless of the number of methotrexate doses given. Vincristine and Asparaginase is to be administered regardless of counts.*

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0.

9.4.1 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push x 5 on **Days 0, 10, 20, 30 and 40**.

9.4.2 Methotrexate

100 mg/m² IVPB IN D_5W 50ml (over 10 to 15 minutes) as initial dose on **Day 0**. Escalate each subsequent dose by 50 mg/m²/dose from previous dose to toxicity (See Section 12.8 for guidelines). A maximum of 5 doses will be administered on Days 0, 10, 20, 30 and 40. The day of methotrexate dose administered can be altered ±1 day in order for it to be given on a weekday.

9.4.3 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 2 doses administered on **Days 1 and 21**.

If PEG asparaginase is not available, substitute native E. coli asparaginase 15,000 IU/m^2 IM x 1 the day after each dose of IV methotrexate is given.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs substitute Erwinia asparaginase 25,000 U/m^2 x 1 the day after each dose of IV methotrexate is given.

If IV methotrexate is held due to neutropenia or thrombocytopenia, the dose of E. coli or Erwinia asparaginase should *not* be withheld. It may be administered on the same day as vincristine is given.

See Section 12.1 for clarification of dose and schedule for substitutions.

9.4.4 Intrathecal Methotrexate

Days 0, 30

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

The volume of CSF removed should be equal to the volume delivered.

9.5 DELAYED INTENSIFICATION I (8 WEEKS) (PHASE IV)

This phase consists of reinduction and reconsolidation therapies. For all patients in remission upon completion of Phase III, Day 0 of Phase IV is Day 56 of Phase III or when the ANC is > 750/μL and the platelet count > 75,000/μL, whichever occurs last**. Once begun, the reinduction and reconsolidation therapies are not interrupted for myelosuppression alone**. Reconsolidation therapy is scheduled to begin on Day 28, but should be delayed until the ANC is > 750/μL and platelets >75,000/μL. **Any serious infection (Varicella, *Pneumocystis carinii* pneumonia) or neutropenia, fever and proven infection warrants chemotherapy interruption at any time during phase IV.** Bone marrows are often difficult to interpret during this phase. Pancytopenia is inevitable and M2 recovery marrows are not uncommon.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0.

9.5.1 Reinduction (4 weeks)

9.5.1.1 Vincristine
1.5 mg/m² (2.0 mg maximum dose) IV push weekly x 3 on **Days 0, 7 and 14**.

9.5.1.2 Doxorubicin
25 mg/m² IVPB (over 15 to 30 mins) through IV infusion in D_5W 50ml weekly x 3 doses on **Days 0, 7, 14.**

9.5.1.3 Dexamethasone
10 mg/m²/day PO x 14 days administered in two or three divided daily doses on **Days 0-6 and 14-20. No taper**.

9.5.1.4 Intrathecal Methotrexate
Day 0

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

The volume of CSF removed should be equal to the volume delivered.

9.5.1.5 L-Asparaginase
Peg-asparaginase 2500 IU/m² IM x 1 dose administered on **Day 3 ± 1 day**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 3, 5, 7, 10, 12 and 14.**

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m²/dose IM may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

9.5.2 Reconsolidation (4 weeks)

9.5.2.1 Cyclophosphamide
1000 mg/m² IVPB (over 30 minutes) in D5W50ml over 30 minutes on **Day 28.**
Reduce urine specific gravity to ≤ 1.015 with IV fluids before each dose. Maintain fluids at twice maintenance for at least 4 hours after each dose.
Use Lasix 0.25-0.5 mg/kg IV for urine output < 3 mL/kg/hr after cyclophosphamide.

9.5.2.2 Mesna
500 mg/m² IVPB should be administered in D5W 50ml 15-30 minutes prior to the cyclophosphamide dose and 3 hours post cyclophosphamide infusion.

9.5.2.3 Thioguanine

60 mg/m²/day PO x 14 days, to be administered at least 1 hr before or 2 hours after evening meal, on **Days 28-41**. Should be taken without milk products. Adjust dose of TG using half-tablet and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 420 mg/m² as possible.

BSA (m^2)	Daily dose per week (1 tab = 40 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.4 - 0.44	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.45 - 0.49	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.5 - 0.54	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.6 - 0.64	1 tab/ d x 6; ½ tab / d x 1	260 mg/wk
0.65 - 0.69	1 tab / day	280 mg/wk
0.70 - 0.74	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
0.75 - 0.79	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
0.8 - 0.84	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
0.85 - 0.89	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
0.9 - 0.94	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
0.95 – 0.99	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
1.0 - 1.04	1½ tab /day	420 mg/wk
1.05 - 1.09	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.10 - 1.14	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.15 - 1.19	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.2 - 1.24	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.25 - 1.29	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.3 - 1.34	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.35 - 1.39	2 tab / day	560 mg/wk
1.4 - 1.44	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
1.45 - 1.49	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
1.5 - 1.54	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
1.55 - 1.59	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
1.60 - 1.64	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
1.65 - 1.69	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
1.7 - 1.74	2½ tab / d	700 mg/wk
1.75 - 1.79	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
1.8 – 1.84	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
1.85 – 1.89	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
1.9- 1.94	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
1.95- 1.99	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
2.0- 2.04	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk

Do not increase dose for ANC > 1500/µL until maintenance therapy.

9.5.2.4 Cytosine Arabinoside (Ara-C)
75 mg/m² IV push or SC x 8 days on **Days 29-32 and 35-38**.

9.5.2.5 Vincristine
1.5 mg/m² (maximum dose 2.0 mg) IV push weekly x 2 on **Days 42 and 49**.

9.5.2.6 L-Asparaginase
Peg-asparaginase 2500 IU/m² IM x 1 dose administered on **Day 42**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 42, 45, 49, 52, 55 and 57.**

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m²/dose IM may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

9.5.2.7 Intrathecal Methotrexate
Days 28 and 35

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

The volume of CSF removed should be equal to at least half the volume delivered.

9.6 INTERIM MAINTENANCE II (CAPIZZI I) (8 WEEKS) (PHASE V)
For all patients in remission upon completion of Phase IV, Day 0 of Phase V will be Day 56 of Phase IV or when peripheral counts recover with ANC > 750/μL and platelet count > 75,000/μL. During Phase V, all therapy should be interrupted for serious infection such as varicella or pneumocystis carinii pneumonia. Only methotrexate should be held for ANC < 750/μL or platelets < 75,000/μL. Methotrexate should be reinstituted on the first due date following the held dose; dosage should be decreased by 20% from the previously administered dose. Missed doses will not be made up. If counts do not recover within 21 days from a methotrexate dose, bone marrow aspiration should be performed, and, if not M3, repeat at 11 day intervals until count recovery or M3. Day 43 of Phase V will be the last day of chemotherapy administration during this phase, regardless of the number of methotrexate doses given.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0

9.6.1 Vincristine
1.5 mg/m² (maximum dose 2.0 mg) IV push x 5 administered on Days 0, 10, 20, 30 and 40.

9.6.2 Methotrexate
100 mg/m² IV push (over 10 to 15 minutes) as initial dose on day 0. Escalate each subsequent dose by 50 mg/m²/dose from previous dose to toxicity.

A maximum of 5 doses will be administered on Days 0, 10, 20, 30 and 40.

9.6.3 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 2 doses administered on **Days 1 and 21**.

If PEG asparaginase is not available, substitute native E. coli asparaginase 15,000 IU/m^2 IM x 1 the day after each dose of IV methotrexate is given.

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs substitute Erwinia asparaginase 25,000 U/m^2 x 1 the day after each dose of IV methotrexate is given.

If IV methotrexate is held due to neutropenia or thrombocytopenia, the dose of E. coli or Erwinia asparaginase should <u>*not*</u> be withheld. It may be administered on the same day as vincristine is given.

See Section 12.1 for clarification of dose and schedule for substitutions.

9.6.4 Intrathecal Methotrexate

Days 0, 30*

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

Doses

*Patients with CNS disease at diagnosis **will not** receive IT methotrexate on Day 30.
The volume of CSF removed should be equal to the volume delivered.

9.7 DELAYED INTENSIFICATION II (8 WEEKS) (PHASE VI)

This phase consists of reinduction and reconsolidation therapies. For all patients in remission upon completion of Phase III, Day 0 of Phase IV is Day 56 of Phase III or when the ANC is > 750/μL and the platelet count > 75,000/μL, whichever occurs last**. Once begun, the reinduction and reconsolidation therapies are not interrupted for myelosuppression alone**. Reconsolidation therapy is scheduled to begin on Day 28, but should be delayed until the ANC is > 750/μL and platelets >75,000/μL. **Any serious infection (Varicella, *Pneumocystis carinii* pneumonia) or neutropenia, fever and proven infection warrants chemotherapy interruption at any time during phase IV.** Bone marrows are often difficult to interpret during this phase. Pancytopenia is inevitable and M2 recovery marrows are not uncommon.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0

9.7.1 Reinduction II (4 weeks)

9.7.1.1 Vincristine

1.5 mg/m^2 (2.0 mg maximum dose) IV push weekly x 3 on **Days 0, 7 and 14**.

9.7.1.2 Doxorubicin

25 mg/m² IVPB (over 15 to 30 mins) through IV infusion in D_5W 50ml weekly x 3 on **Days 0, 7, 14.**

9.7.1.3 Dexamethasone

10 mg/m²/day PO x 14 days administered in two or three divided daily doses on **Days 0-6 and 14-20. No taper.**

9.7.1.4 Intrathecal Methotrexate

Day 0

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

The volume of CSF removed should be equal to the volume delivered.

9.7.1.5 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 3 ± 1 day**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 3, 5, 7, 10, 12 and 14.**

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

9.7.2 Reconsolidation II (4 weeks)

9.7.2.1 Cyclophosphamide

1000 mg/m² IVPB (over 30 minutes) in D5W50ml over 30 minutes on **Day 28.**
Reduce urine specific gravity to ≤ 1.015 with IV fluids before each dose. Maintain fluids at twice maintenance for at least 4 hours after each dose.
Use Lasix 0.25-0.5 mg/kg IV for urine output < 3 mL/kg/hr after cyclophosphamide.

9.7.2.2 Mesna

500 mg/m² IVPB in D5w50ml should be administered 15-30 minutes prior to the cyclophosphamide dose and again 3 hours post cyclophosphamide infusion on **day 28.**

9.7.2.3 Thioguanine

60 mg/m²/day PO x 14 days, to be administered at least 1 hr before or 2 hours after evening meal, on **Days 28-41**. Should be taken without milk products. Adjust dose of TG using half-tablet and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 420 mg/m² as possible.

BSA (m^2)	Daily dose per week (1 tab = 40 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.4 - 0.44	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.45 - 0.49	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.5 - 0.54	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.6 - 0.64	1 tab/ d x 6; ½ tab / d x 1	260 mg/wk
0.65 - 0.69	1 tab / day	280 mg/wk
0.70 - 0.74	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
0.75 - 0.79	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
0.8 - 0.84	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
0.85 - 0.89	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
0.9 - 0.94	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
0.95 – 0.99	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
1.0 - 1.04	1½ tab /day	420 mg/wk
1.05 - 1.09	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.10 - 1.14	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.15 - 1.19	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.2 - 1.24	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.25 - 1.29	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.3 - 1.34	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.35 - 1.39	2 tab / day	560 mg/wk
1.4 - 1.44	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
1.45 - 1.49	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
1.5 - 1.54	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
1.55 - 1.59	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
1.60 - 1.64	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
1.65 - 1.69	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
1.7 - 1.74	2½ tab / d	700 mg/wk
1.75 - 1.79	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
1.8 – 1.84	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
1.85 – 1.89	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
1.9- 1.94	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
1.95- 1.99	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
2.0- 2.04	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk

Do not increase dose for ANC > 1500/µL until maintenance therapy.

9.7.2.4 Cytosine Arabinoside (Ara-C)

75 mg/m² IV push or SC x 8 days on **Days 29-32 and 35-38**.

9.7.2.5 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push weekly x 2 on **Days 42 and 49**.

9.7.2.6 L-Asparaginase

Peg-asparaginase 2500 IU/m^2 IM x 1 dose administered on **Day 42**.

If Peg-asparaginase is not available native *E. coli* L-asparaginase at 6000 IU/m² IM x 6 doses administered thrice weekly on a Sat-Mon-Wed schedule can be used. Administration days should be approximately as follows: **Days 42, 45, 49, 52, 55 and 57.**

If E. coli asparaginase is unavailable or an objective hypersensitivity reaction occurs Erwinia asparaginase 10,000 IU/m^2/dose IM may be substituted. Erwinia asparaginase should be administered on alternate days without any breaks being given for weekends or holidays (see Section 12.1 for a review of doses and schedule for substitutions).

9.7.2.7 Intrathecal Methotrexate

Days 28 and 35*

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

*Patients with CNS disease at diagnosis **will not** receive IT methotrexate on Day 35.
The volume of CSF removed should be equal to the volume delivered.

9.8 MAINTENANCE - (PHASE V) (12 WEEKS PER COURSE)

9.8.1 Duration

Maintenance begins when the patient has recovered from Delayed Intensification with recovery of peripheral counts with ANC > 750/µL and platelets > 75,000/µL.
The duration of Maintenance will be 2 calendar years for girls and 3 years for boys as measured from the time the patient started Interim Maintenance. The course in progress is stopped when the end therapy date is reached and that course is not completed.

9.8.2 Bone Marrow Aspirations

Routine bone marrow aspirates will not be obtained. ***Bone marrow aspirate should be performed if the patient has***:

1. Circulating blast cells
2. Unexplained organomegaly or lymphadenopathy
3. Unexplained bone pain
4. Documented or suspected extramedullary leukemia
5. Continued ANC < 750/µL or platelets < 75,000/µL more than 2 weeks after stopping chemotherapy for low counts.

Patients are off therapy if they develop an M3 marrow or extramedullary disease at any time while receiving therapy.

9.8.3 Dose Adjustments

Only MP and MTX will be interrupted for myelosuppression (see Section 12.9). The omitted doses will not be made up. The oral doses of MP and MTX should be adjusted to maintain ANC between 750/µL and 1500/µL and platelets ≥ 75,000/µL.

Dosage modifications for toxicity for all treatment phases are detailed in Section 12.0

9.8.4 Maintenance Chemotherapy

9.8.4.1 Intrathecal Methotrexate

Day 0 of each course.

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

The volume of CSF removed should be equal to the volume delivered.

9.8.4.2 Vincristine

1.5 mg/m² (maximum dose 2.0 mg) IV push x 3 on **Days 0, 28, 56.**

9.8.4.3 Dexamethasone

6 mg/m² PO divided TID x 5 days every 28 days on **Days 0-4, 28-32, 56-60**. Patients over 10 years of age should not receive Dexamethasone and should instead receive Prednisone (40 mg/m²/day). Patients who are initially less than 10 years of age should be changed to Prednisone following their 10th birthday.

9.8.4.4 Mercaptopurine (MP)

75 mg/m²/day PO daily to be administered at least 1 hr before or 2 hours after evening meal on **Days 0-83**. Should be taken without milk products. Adjust dose of MP using half-tablet and different doses on alternating days as follows, to attain a weekly cumulative dose as close to 525 mg/m² as possible.

BSA (m^2)	Daily dose per week (1 tab = 50 mg)	Weekly cumulative dose
0.35 - 0.39	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.4 - 0.44	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
0.45 - 0.5	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
0.51 - 0.55	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.56 - 0.6	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.61 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / d x 7	350 mg/wk
0.7 - 0.74	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.75 - 0.78	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
0.79 - 0.82	1 ½ tab / d x 3; 1 tab / d x 4	425 mg/wk
0.83 - 0.87	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.88 – 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 – 0.97	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
0.98 - 1.02	1 ½ tab / d x 7	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.12	2 tab / d x 2; 1½ tab / d x 5	575 mg/wk
1.13 - 1.16	2 tab / d x 3; 1½ tab / d x 4	600 mg/wk

1.17 - 1.2	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.21 - 1.25	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.26 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / d x 7	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2½ tab / d x 2; 2 tab / d x 5	750 mg/wk
1.46 - 1.50	2½ tab / d x 3; 2 tab / d x 4	775 mg/wk
1.51 - 1.55	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.56 - 1.59	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
1.60 - 1.64	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
1.65 - 1.69	2½ tab / d x 7	875 mg/wk
1.70 – 1.74	2 ½ tab /d x 6; 3 tab /d x 1	900 mg/wk
1.75- 1.78	2 ½ tab /d x 5; 3 tab /d x 2	925 mg/wk
1.79- 1.83	2 ½ tab /d x 4; 3 tab /d x 3	950 mg/wk
1.84- 1.88	2 ½ tab /d x 3; 3 tab /d x 4	975 mg/wk
1.89- 1.92	2 ½ tab /d x 2; 3 tab /d x 5	1000 mg/wk
1.93- 1.97	2 ½ tab /d x 1; 3 tab /d x 6	1025 mg/wk
1.98- 2.01	3 tab /d x 7	1050 mg/wk

9.8.4.5 Methotrexate

20 mg/m²/dose PO weekly (escalate as per Section 12.9) to be administered on **Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77.**

9.9 End of Therapy

Therapy will end for patients as follows:
1) Girls will end therapy 2 years from the beginning of Interim Maintenance (I).
2) Boys will end therapy 3 years from the beginning of Interim Maintenance (I).
3) Therapy will end at the anniversary date and the course in progress will **NOT** be completed.

Low Risk Pre T-ALL Protocol

(PALL08-TLR/ CCG 1961 Arm C with HDMTX)

10.0 High risk T-cell ALL Protocol (PALL08-TLR)

10.1 Treatment plan

Patients with T cell ALL who are categorized as low risk (LR) (See Section 3.2) will be treated according to the protocol for high risk Pre B-ALL HR (PALL08 HR) except during the Phase III (Interim Maintenance). During this phase patients with LR T-ALL will receive high dose methotrexate instead of the escalating dose methotrexate with L-asparaginase (Capizzi I). Like the HR Pre-B ALL patients these patients will also receive a single delayed intensification and no radiation therapy.

Please follow the guidelines provided in the PALL08-HR protocol for all phases except Interim Maintenance (Phase III). Details of therapy for this phase are provided below.

Induction Therapy: Phase I (DAYS 0 – 28) *As per Section 8.2*

Consolidation: (Phase II) (9 weeks) *As per Section 8.3*

Interim Maintenance: (HDMTX/MP) (Phase III) (8 weeks) See below

Delayed Intensification: (Phase IV) (8 weeks) *As per Section 8.5*

Maintenance: (Phase V) (12 weeks per course) *As per Section 8.6*

10.2 INTERIM MAINTENANCE (8 WEEKS) (PHASE III)

For all patients in remission upon completion of Phase II, Day 0 of Phase III will be Day 63 of Phase II or when peripheral counts recover with ANC > 750/μL and platelet count > 75,000/μL. ALT < 20X the upper limit of normal; direct bilirubin and creatnine normal for age.

10.2.1 Mercaptopurine (MP)

25 mg/m²/day PO daily to be administered at least 1 hr before or 2 hours after evening meal on **Days 0-56**. It should be taken without milk products Adjust dose of MP using half-tablet and different doses on alternating days or use liquid suspension formulation to attain a weekly cumulative dose as close to 175 mg/m² as possible.

10.2.2 Intrathecal Methotrexate

Days 7, 21, 35 and 49

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

The volume of CSF removed should be equal to the volume delivered.

10.2.3 High Dose Methotrexate Infusion (HDMTX)

Days 7, 21, 35 and 49

Hold TMP-SMX on the days of HDMTX infusion and for at least 72 hours after the start of the HDMTX infusion and until the MTX level is less than 0.4 μM. *In the presence of delayed clearance continue to hold TMP-SMX until MTX level is less than 0.1 μM*

Hold any non-steroidal anti-inflammatory medications, penicillin, Tazocin or aspirin-containing medications on the day of HDMTX infusion and for at least 72 hours after the start of the HDMTX infusion and until the MTX level is less than 0.4 μM. *In the presence of delayed clearance continue to hold all these medications until MTX level is less than 0.1 μM*

Prehydrate with D5 ¼ NS with 40 mEq $NaHCO_3$/L at 125 mL/m^2/hour for at least 6 hours and until urine specific gravity is ≤1.010 and pH is ≥7.0 and ≤8.0. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. Give a bicarbonate bolus (25 mEq/m^2 over 15 min) to raise the urine pH relatively quickly. Continue hydration and alkalinization throughout HDMTX infusion, and for a minimum of 48 hours

after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 μM.

Hour 0: *Methotrexate infusion should begin prior to 1100 a.m. In case of a delay in initiation of the MTX beyond 1100 a.m. the infusion should be postponed until the next day.* MTX 500 mg/m^2 IV mixed in a final volume of 100 ml of D5W over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 mixed in a final volume of 1000 ml D5 ¼ NS with 40 mEq $NaHCO_3$/L given by continuous IV infusion over 23.5 hours at 42.5 ml/hr. Be certain that the HDMTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Hours 24, 36 and 48: Draw MTX level and serum creatinine at 24, 36 and 48 hours from the start of the MTX infusion. Therefore the first MTX level will be drawn immediately following the completion of the infusion.

If the 24 hour level is <150 μM continue with standard Leucovorin rescue protocol, beginning with 15 mg/m^2 IV/PO at hour 48 (24 hours following completion of MTX infusion) to be administered every 6 hours. Adjust the dose based on the table below once the Hour 48 MTX level is available.

If the 24 hour level is >150 μM and/or creatinine >125% baseline, initiate Leucovorin rescue immediately at 100 mg/m^2 IV every 6 hours, and follow the results of levels drawn at Hour 36 and 48.

Leucovorin rescue adjustments should be made based on the Hour 48 level as outlined in the table below:

Time from start of MTX infusion	MTX level (μM)	Leucovorin dose
48 hours	< 0.5 μM	10 mg/m^2 IV/PO q 6 hours
48 hours	> 0.5 to 5 μM	15 mg/m^2 IV/PO q 6 hours
48 hours	> 5 to 19.9 μM	15 mg/m^2 IV/PO q 3 hours
48 hours	20 to 100 μM	100 mg/m^2 IV/PO q 6 hours
48 hours	> 100 μM	1000 mg/m^2 IV/PO q 6 hours

In addition increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value >7.0 and monitor urine output to determine if volume is > 80% of the fluid intake, measured every 12 hours.
If serum creatinine rises significantly, at any time point, assure appropriate urine pH and urine volume as above. If urine output fails to continue at 80% of the fluid intake, consider furosemide.

Continue to check MTX levels at least once every 24 hours until the level is <0.1 μM. At this time the leucovorin rescue and hydration can be discontinued.

For leucovorin rescue adjustment at other time points refer to the graph below and consult with the clinical pharmacist.

When IT therapy and HDMTX are scheduled for the same day, deliver the IT therapy within six hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).

For subsequent courses:
• DO NOT EXTEND leucovorin or modify subsequent courses if patient did not experience >Grade 2 mucositis or >1 week delay in administration of chemotherapy. If patient again has delayed clearance, follow guidelines and monitor for toxicity.

• If patient experienced Grade 2 clinical toxicity and 48 hour MTX level was > 0.18 but <5 μM then increase hydration to a rate of 200 mL/m^2/hour prior to, during, and for at least 24 hours immediately following HDMTX for next course.

• If patient experienced Grade 3 or 4 clinical toxicity and 48 hour MTX level was > 0.18 but < 5 μM, then reduce dose of MTX by 25% of the original dose (i.e. 3.75 gm/m^2/dose; with 10% dose as bolus and 90% dose as infusion) for next course, maintaining hydration at 200 mL/m^2/hour and following leucovorin rescue schedule as above.

If patient has delayed clearance (Hour 48 level ≥ 5 μM) and Grade 3 or 4 toxicity after reduced dose, then decrease next course to 50% of original dose.

If patient has adequate clearance or ≤ Grade 2 toxicity escalate dose in 25% increments back to the original doses as able with subsequent courses.

Management of the patient with markedly delayed MTX clearance:
For patients who have delayed clearance of MTX, defined by 48 hour level > 5 μM OR 72 hour level > 0.5 μM, follow the guidelines given above. ***In addition, for subsequent courses***:

• If patient experienced Grade 2 or less clinical toxicity then increase hydration to a rate of 200 mL/m^2/hour prior to, during, and for 24 hours immediately following HDMTX for next course and dose reduce HDMTX by 25% of the original dose (i.e. 3.75 gm/m^2/dose; with 10% dose as bolus and 90% dose as infusion) with leucovorin as above. If tolerated without delayed excretion, increase MTX dose by 25% for each course until full dose achieved.

• If patient experienced Grade 3 or 4 clinical toxicity then reduce dose of MTX by 50% of the original dose (i.e. 2.5 gm/m^2/dose; with 10% dose as bolus and 90% dose as infusion) for next course maintaining hydration at 200 mL/m^2/hour and following original leucovorin rescue schedule as above. Discuss with consultant and protocol coordinator if patient still has delayed clearance or Grade III or IV toxicity. If patient has adequate clearance and ≤ Grade 2 toxicity with the reduced dose course then escalate dose by 25% (of the original dose) for each course until administration of full dose MTX achieved.

• For patients with MTX level > 10 μM more than 48 hours after beginning MTX or with a creatinine > 1.5 x normal or with a calculated creatinine clearance < 60 mL/m^2/min and delayed MTX excretion, notify consultant and protocol coordinator for discussion regarding further MTX administration. This decision has to be taken in consultation with the Clinical Pharmacist.

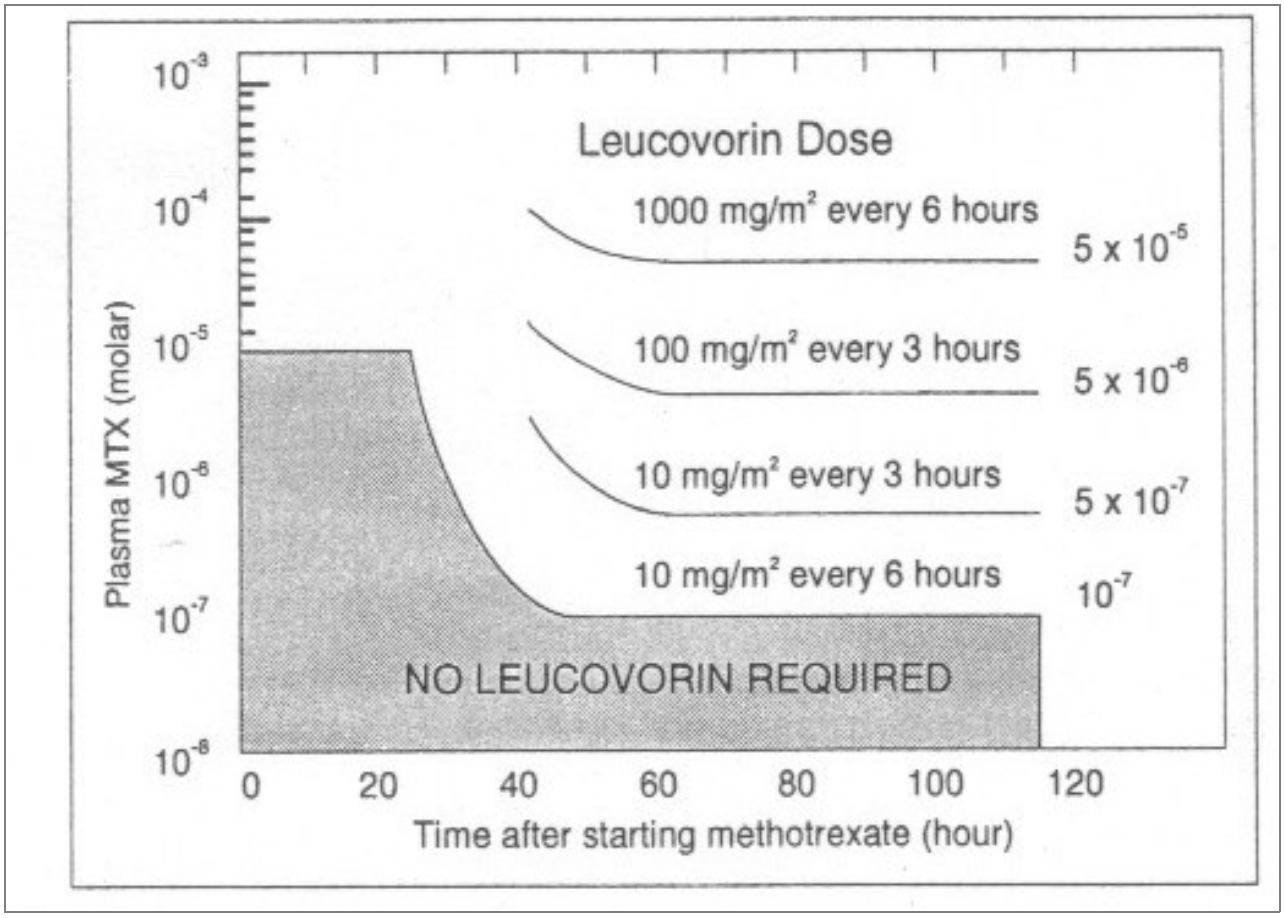
Management of the patient with clinical toxicity despite appropriate MTX clearance:

• If mucositis ≥ Grade 3 develops despite an appropriate fall in MTX level begin leucovorin rescue at hour 36 from the START of HDMTX infusion at a dose of 75 mg/m^2 IV x 1, then 15 mg/m^2 every 3 hours x 4, then every 6 hours until MTX level < 0.08 μM. Also increase hydration to a rate of 200 mL/m^2/hour with alkalinization as above.

• If mucositis occurs despite increased leucovorin rescue, decrease MTX dose by 25% (of the original dose) in the subsequent course and resume standard dose leucovorin as above.

• If subsequent course is not associated with mucositis resume original leucovorin rescue and attempt to increase to full dose MTX during next course.

MTX-Leucovorin Graph



Conversion key

$1x10^{-6}$ M= 1 μM,
$5x10^{-5}$ M = 50 μM,
$5x10^{-7}$M = 0.5μM,
$1x10^{-7}$M = 0.1μM
10^{-8}M =0.01μM

High Risk T-ALL Protocol

(PALL08-THR/ CCG 1961 Arm D with HDMTX)

11.0 Very High risk T-cell ALL Protocol (PALL08-THR)

11.1 Treatment plan

Patients with T cell ALL who are categorized as high risk (HR) (See Section 3.2) will be treated according to the protocol for very high risk Pre B-ALL (PALL08-VHR) except during the Phase III (Interim Maintenance I). During this phase patients with HR T-ALL will receive high dose methotrexate instead of the escalating dose methotrexate with L-asparaginase (Capizzi I). Like the VHR Pre-B ALL patients these patients will also receive double delayed intensification. The second Interim Maintenance for these patients (Interim Maintenance II; Phase V) will be with escalating dose methotrexate and L-asparaginase (Capizzi I) as for the Pre-B ALL patients.

All patients with CNS leukemia (CNS3 status, cranial nerve palsy or brain parenchymal infiltrates) will receive radiation therapy to the craniospinal field during the first cycle of Maintenance therapy. Patients who are CNS negative will receive cranial prophylactic radiation therapy during this same phase.

Please follow the guidelines provided in the PALL08-VHR protocol for all phases except Interim Maintenance I (Phase III). Details of therapy for this phase are provided in Section 10.2 for the protocol PALL08-TLR.

Induction Therapy: Phase I (DAYS 0 – 28) *As per Section 9.2*

Consolidation: (Phase II) (9 weeks) *As per Section 9.3*

Interim Maintenance I: (HDMTX/MP) (Phase III) (8 weeks) *as per Section 10.2*

Delayed Intensification I: (Phase IV) (8 weeks) *As per Section 9.5*

Interim Maintenance II (Capizzi I) (Phase V) (8 weeks) *As per Section9.6*

Delayed Intensification II (8 weeks) (Phase VI) *As per Section 9.7*

Maintenance: (Phase VII) (12 weeks per course) *As per Section 9.8*

12.0 DOSING AND DOSE MODIFICATION FOR TOXICITIES

These guidelines have been prepared through review of the local protocols as well as protocols from the Children's Cancer Group, Pediatric Oncology Group, and Children's Oncology Group. Please notify the treating consultant and study coordinator if a patient develops a toxicity necessitating removal from protocol. The drugs are listed in alphabetical order:

12.1 Asparaginase

ALLERGY

Local (inflammation at injection site, swelling, transient flushing or rash, drug fever < 38C) – Continue PEG or E.coli. Do NOT premedicate with antihistamines as it may mask the appearance of systemic allergy. Systemic allergy is associated with the presence of asparaginase neutralizing antibodies, which may render asparaginase therapy ineffective. If recurrent reactions occur substitute with Erwinia if available. If not available discontinue asparaginase. If patient develops systemic allergy to Erwinia, discontinue all asparaginase therapy.
Anaphylaxis/Systemic Allergic reactions: Discontinue Pegasparaginase or E.coli if systemic allergic reaction (urticaria, wheezing, laryngospasm, hypotension, etc) occurs.
Induction: Substitute with Erwinia asparaginase 10,000 IU/m^2 IM to complete the 9 doses on an every other day schedule (including weekends and holidays).
Consolidation/Delayed intensification: Substitute Erwinea asparaginase 10,000 IU/m^2 IM for every dose of E. coli asparaginase, to be administered on an every other day schedule (including weekends and holidays).
Interim Maintenance: Substitute Erwinea asparaginase 25,000 IU/m^2 IM for every dose of E. coli asparaginase.

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

HYPERBILIRUBINEMIA - No specific guidelines available. May need to withhold dose if direct bilirubin elevated.

HYPERGLYCEMIA/HYPERLIPIDEMIA - Do NOT modify dose

KETOACIDOSIS – hold until blood glucose can be regulated with insulin

PANCREATITIS (Grade 2 – 4) – Discontinue asparaginase if hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and amylase elevation 2 x ULN (Grade 3)). In mild pancreatitis hold until symptoms and signs subside and amylase levels return

to normal and then resume. Severe pancreatitis is a CONTRAINDICATION to additional asparaginase administration.

THROMBOSIS – Withhold until resolved. Give appropriate antithrombotic therapy as indicated. Resume on resolution of symptoms while continuing LMWH or antithrombotic therapy. For significant thrombosis (not line related) consider evaluation for inherited predisposition to thrombosis.

CNS EVENTS (bleed, thrombosis, or infarction) – Hold asparginase. Treat with FFP, factors or anticoagulation. Resume full dose when all symptoms resolve and improving radiological evaluations. Consider evaluation for inherited predisposition to thrombosis.

12.2 Cyclophosphamide

HEMATURIA – Omit if *macroscopic* hematuria. If there is previous history of significant hematuria, hydrate before cyclophosphamide until specific gravity < 1.015 and continue to hydrate at 125 ml/m^2/hr for 24 hours after dose. Give IV Mesna (200 mg/m^2) 15 minutes before the cyclophosphamide and repeat at hours 3, 6, and 9. MESNA may also be given by continuous infusion.

ACUTE FLUID RETENTION (SIADH) – Treat with furosemide and saline; Do NOT modify cyclophosphamide administration.

12.3 Cytarabine (Ara-C)

ARA-C SYNDROME (fever) – Do NOT withhold Ara-C for fever if it is likely to have been caused by the Ara-C. Obtain blood cultures if a central line is present. For rash or conjunctivitis, withhold for Grade 3/4 toxicity until resolved. MAKE UP MISSED DOSES and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis. Once Consolidation or Delayed Intensification has started DO NOT INTERRUPT for uncomplicated myelosuppression; DO HOLD for proven or presumed SERIOUS infection. DO MAKE UP DOSES if the interruption has been less than 3 doses. If 3 or more doses have been missed due to the febrile/neutropenic episode, restart chemotherapy at the next block of Cytarabine/thiopurine.

12.4 Daunorubicin and Doxorubicin (Anthracyclines)

CARDIAC TOXICITY – Discontinue for clinical or echocardiographic evidence of cardiomyopathy (shortening fraction (SF) < 27% or EF < 50%).

MYELOSUPPRESSION (beyond induction) – For patients with severe infection or severe mucositis (Grade 3/4) with an ANC < 500/µl, anthracycline should be delayed during all phases other than induction. During induction, continue with anthracycline administration. Subsequent doses should be given at *full dose*. Doxorubicin may be delayed up to 1 week in DI#1 and DI#2 and given at *full dose* once resolved. However, if

the delay exceeds one week DO NOT give the delayed dose. Treatment with dexamethasone and vincristine should continue on schedule. Cyclophosphamide will still begin on day 28 provided blood count criteria are satisfied.
INFECTION – For presumed or proven SERIOUS infection either or both of the 3rd and 4th dose may be delayed or omitted; however, subsequent doses should be given at full dose.

HYPERBILIRUBINEMIA:

DIRECT BILIRUBIN	% DOSE REDUCTION
< 25 µmol/L 1.2 mg/dl	Full Dose
25-50 µmol/L 1.2 – 3 mg/dl	50%
51-85 µmol/L 3.1 – 5 mg/dl	75%
>85 µmol/L	Hold dose

> 85 µmol/L - Withhold dose until toxicity resolved. Do NOT make up missed doses
If elevation persists > 1 month, exclude infectious hepatitis or other causes of hyperbilirubinemia.

EXTRAVASATION – In the event of extravasation consider the following:
a. Stop infusion, aspirate drug and blood if possible, remove needle.
b. Apply DMSO (concentrations 99%) topical solution to area twice that affected by extravasation. Allow DMSO to air dry. Do NOT cover. Repeat QID for 7–14 days.
c. Elevate limb if possible.
d. Apply ice pack for one hour, can repeat up to QID for 24 hours.
e. Injecting steroids is recommended by some.
Institutional extravasation guidelines, if available, will supersede the above recommendations.

12.5 Intrathecal Cytarabine

Do NOT withhold dose given on day 1 of induction in front-line protocols.
Note: If neurological examination is abnormal or history of recent trauma to the head consider neuro-imaging prior to intrathecal therapy.

12.6 Intrathecal Methotrexate:

SYSTEMIC TOXICITY – Do NOT reduce dose for systemic toxicity (myelosuppression, mucositis, etc.). Instead, leucovorin may be used at a dose of 5 mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC< 500/ul) or mucositis. Do NOT administer leucovorin solely to prevent myelosuppression. For patients with DOWN SYNDROME, leucovorin should be administered after every dose of IT MTX during ALL phases of therapy EXCEPT Maintenance.

NEUROTOXICITY – Acute neurotoxicity may range from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies. These toxicities are poorly understood and currently it is impossible to predict who will suffer these complications. In addition, there are no data clearly linking the occurrence of an acute neurotoxic event with an increased risk of long-term neurocognitive dysfunction, nor do changes present on MRI at the time of an acute event clearly correlate with or predict outcome. The exclusive use of IT Ara-C has not been studied or described in the context of ALL therapy nor can one demonstrate the safety of omitting multiple doses of IT therapy without concomitant use of cranial irradiation or high dose methotrexate. Many acute events are temporally related to intrathecal therapy and commonly occur 9–11 days after the IT administration. If an acute event develops the following are guidelines that should be considered:

a. Take history and physical examination.
b. Neurology consultation.
c. Exclude other causes (fever, infection, electrolyte, thrombocytopenia, narcotic and drugs, etc.).
d. Imaging (CT and/or MRI) – some findings may be suggestive of chemotherapy effect (Calcifications on CT scan may indicate a more severe mineralizing leukoencephalopathy or posterior reversible encephalopathy on MRI with extensive diffusion abnormalities, but these do not seem to correlate with subsequent demyelination or gliosis)
e. Consider additional studies (MRA/MRV) if clinically indicated (e.g. Focal deficits).
f. Hold next dose of IT therapy.
g. Consider substituting with IT Ara-C for one dose.
h. Consider Leucovorin rescue 5 mg/m^2 q 12hrs x 2 doses beginning 48 hours after the LP.
i. If events do not recur, resume standard therapy following one omitted/modified IT dose.
j. If recurrent or progressive then another evaluation is warranted and consider a more prolonged or definitive change in therapy.

HYDROCEPHALUS, MICROCEPHALY OR KNOWN CSF FLOW ABNORMALITY PRECLUDING IT CHEMTHERAPY VIA LUMBAR PUNCTURE.
Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, BUT AT 50% OF THE CORRESPONDING AGE-BASED DOSES that would be given by LP. Patients who are extremely obese or have other physical abnormalities that make conducting a lumbar puncture impossible/very difficult may also be considered for Ommaya reservoir placement and Intraventricular therapy.

VIRAL, BACTERIAL, OR FUNGAL MENINGITIS – Omit until resolved.

12.7 High-Dose Methotrexate (HDMTX) and Leucovorin Rescue:

INFUSION GUIDELINES (for details refer to the guidelines for HDMTX infusion; Section 10.2)

When IT MTX and HDMTX are scheduled for the same day, deliver IT MTX **WITHIN** 6 hours of the beginning of the IV MTX (hour – 6 to + 6, with **0 being the start of the MTX bolus**).

Hold TMP-SMX (Septra), penicillin, or any anti-inflammatory medication on the day of HDMTX and for 72 hours after the start of HDMTX or until MTX level is < 0.1 μM whichever comes last (it maybe easier to hold these during Interim maintenance depending on patient education and communication).

Prehydrate: D5 ¼ NS + 30 mEq $NaHCO_3$/L at 125 ml/m^2/hr x 6 hours minimum and until urine specific gravity is ≤ 1.010 and pH ≥ 7.0 and ≤8.0. Adjust fluid volume and sodium bicarbonate to maintain these parameters. Give $NaHCO_3$ bolus (25 mEq/m^2) over 15 minutes to raise the urine pH relatively quickly. Continue hydration and alkalinization throughout HDMTX infusion and for a minimum of 48 hours after its completion or until MTX level < 0.1μM.

HOUR 0: MTX 500 mg/m^2 + D5 ¼ NS + 30 mEq $NaHCO_3$/L (total volume 65 ml/m^2) infused as a bolus over 30 minutes. Followed immediately by MTX 4500 mg/m^2 + D5 ¼ NS + 30 mEq $NaHCO_3$/L (total volume 2935 ml/m^2) by continuous IV infusion over 23.5 hours at 125 ml/m^2/hr. Infusion MUST be completed in the 24 hour period.

Monitor intake and urine output and pH every 4 hours. Adjust hydration to 200 ml/m^2/hr if output is < 80% of intake. Consider furosemide if urine output remains <80% despite increasing hydration. Maintain urine pH of 7 – 8.

Check MTX level and serum creatinine at Hour 24, 36 and 48.

If **Hour 24** MTX level ≥ 150 μM and/or creatinine > 125% baseline then increase hydration to 200 ml/m^2/hr.

NEPHROTOXICITY: IF PRETREATMENT serum creatinine >1.5 x baseline or GFR < 65 ml/minute/1.73m^2 POSTPONE course until recovery. If renal function does not recover, OMIT MTX. Do NOT give HDMTX to a patient with this degree of renal impairment. *Replacement of HDMTX with lower doses should be discussed with the study coordinator.*

LIVER DYSFUNCTION: Check ALT and Direct bilirubin level immediately PRIOR to each course of IV MTX. Hold IV MTX for direct bilirubin >25 μmol/L. For ALT levels follow guidelines in the table below:

ALT	**IV MTX**
X ULN (450 10 > (Units/L	Continue therapy as scheduled
X ULN (450- 20 – 10 (900 Units/L	Continue therapy as scheduled for 1 cycle
X ULN for 2 20 – 10 consecutive cycles ((450-900 Units/L	Discontinue TMP/SMX Hold therapy until ALT < 10 X ULN, then resume at full (doses at point of interruption (the clock stops Do NOT skip doses
X ULN (900 20 < (Units/L	Hold therapy until ALT < 10 X ULN, then resume at full .doses at point of interruption Do NOT skip doses
X ULN (900 20 < Units/L) for > 2 weeks	Evaluate with AST, Bili, Alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV .serologies .Consider liver biopsy before additional therapy given Notify treating consultant and study coordinator

MUCOSITIS: Withhold for GRADE 3/4 mucositis until resolved. Increase leucovorin rescue following next course from 3 to 5 doses on a q 6 hr schedule. If mucositis recurs despite extending leucovorin then DECREASE the dose of MTX by 25%, increase hydration to 200 ml/m^2/hr and continue increased leucovorin as above. Consider culturing lesions for herpes simplex if mucositis persists or recurs and empirically starting acyclovir. IF subsequent doses are well tolerated use a stepwise approach to resuming standard dose.

MYELOSUPPRESSION: Hold TMP/SMX (Septra) for myelosuppression, alternative prophylaxis with dapsone (1–2 mg/kg/day, maximum 100 mg/day), aerosolized (300 mg/ q month ≥ 5 years of age) or IV (4mg/kg per month) pentamidine, or atovaquone (30 mg/ kg/day if 1-3 months or > 2 years, 45 mg/kg/day if between 3 months and 2 years) may be considered.

If prolonged neutropenia (ANC < 750 for > 7 days) despite discontinuation of TMP/SMX OR prolonged thrombocytopenia (platelets < 75 for > 7 days) then hold the mercaptopurine (MP) until recovery and then administer IV MTX and MP at full dose. If myelosuppression recurs with these modifications then reduce MTX dose by 20%.

12.8 Capizzi Methotrexate

LIVER DYSFUNCTION and NEPHROTOXICITY as above.

MUCOSITIS: Withhold for GRADE 3–4 mucositis until resolved. Discontinue MTX dose escalation and resume at 80% of last dose **if therapy is delayed for myelosuppression or GRADE 3 or greater mucositis**. If mucositis persists or recurs consider culturing lesions for herpes simplex and empirically starting acyclovir.

MYELOSUPPRESSION

1. ANC >750 and Platelets >75, proceed with all chemotherapy and dose escalation of methotrexate as indicated.
2. ANC<750 or Platelets <75, omit methotrexate and proceed with vincristine and L-asparaginase at full dose according to protocol.
3. If ANC>750 and Platelets >75 at the next scheduled dose following the missed dose, give full doses of vincristine and L-asparaginase and administer methotrexate at a dose 20% less than the last dose administered. DO NOT MAKE UP MISSED DOSES OF MTX.
4. If ANC >750 and Platelets >75 at subsequent scheduled dates continue to escalate the methotrexate dose by 50 mg/m^2.
5. Total duration of Interim Maintenance should not exceed 43 days.

12.9 Weekly PO Methotrexate and Daily 6-Mercaptopurine

For Consolidation (PALL08-LR), and Maintenance for all protocols:

a. ANC ≥ 750 and < 1000 and/or Platelets ≥ 75 and < 100 – Do NOT modify dose and check CBC weekly x 4 if no change continue 100 % dose and monitor count every 2 – 4 weeks.
b. ANC ≥ 500 and < 750 and/or Platelets ≥ 50 and < 75 – Reduce dose to 50% original dose until ANC ≥ 750 and Platelets ≥ 75. Increase dose gradually every 2 weeks to 75% and then 100% provided that ANC remains ≥ 750 and Platelets ≥ 75.
c. ANC < 500 and/or Platelets < 50 – Discontinue dose until ANC ≥ 750 and Platelets ≥ 75. Restart 6MP and/or MTX at 50% dosing on the day counts recover. Increase dose gradually every 2 weeks to 75% and then 100% provided that ANC remains ≥ 750 and Platelets ≥ 75.

NOTE: In case of prolonged myelosuppression (> 2 weeks despite discontinuing therapy) consider performing a bone marrow aspiration after 2 weeks of withholding therapy. However, if viral myelosuppression is clinically suspected and monocytes increasing then bone marrow aspiration may be omitted or postponed up to 4 weeks after therapy is withheld.

Consider discontinuing TMP/SMZ if recurrent and use alternative prophylaxis. DO NOT MAKE UP MISSED DOSES (the clock does not stop).

Escalation of Mercaptopurine (MP) and Methotrexate (MTX) for ANC > 1500/μL during Maintenance

The oral doses of MP and MTX should be adjusted to maintain the ANC between 750/μL and 1500/μL and the platelet count > 75,000/μL. If the ANC is >1500/μL (and platelets > 75,000/μL) on Day 0 of any maintenance course and the ANC was > 1500/μL on Days 0, 28 and 56 of the preceding course (and platelets were > 75,000/μL), the dose of **MP** should be escalated by 25% (from 75 mg/m²/day to 93.75 mg/m²/day). If the subsequent monthly ANC is:

a. ANC > 750/μL and < 1500/μL (and platelets > 75,000/μL), keep MP at the 125% dose.
b. ANC < 750/μL and > 500/μL. If the absolute neutrophil count falls to between 500/ μL and 750/μL or platelets < 75,000/μL, MP should be reduced to 50% of original dose until the ANC recovers to ≥ 750/μL at which time MP should be increased to 75% of the original dose and then to full dose one week later, should the ANC remain ≥ 750/μL.
c. ANC > 1500/μL (and platelets > 75,000/μL), keep MP at 125% dose and increase methotrexate by 25% to 25 mg/m²/dose.
d. Continue to increase the MP dose at Day 0 of each maintenance course as outlined above if ANC > 1500/μL persists. Continue to increase the methotrexate dose one month later if ANC > 1500/μL as outlined above. There are no maximum doses for MP and methotrexate.

Consider observing the administration of an oral dose of MTX and checking MTX level 2–4 hours later.

MUCOSITIS Grade 3 – 4: Reduce MTX by 50% for GRADE 3, Withhold for GRADE 4 until resolution then resume at 50% dose with gradual dose escalation. Consider culturing for herpes simplex and empirically starting acyclovir.
SEVERE DIARRHEA OR PERSISTENT VOMITTING: If either develops, MTX should be discontinued and resumed at 50% dosing when symptoms resolved for one week. Escalate gradually as tolerated.

LIVER DYSFUNCITON: For ALT or AST > 5 X ULN (900 Units/L) (GRADE 3 toxicity), obtain total bilirubin. Monitor every 2 weeks during CONSOLIDATION and every 4 weeks during Maintenance as long as ALT/AST remain >5 X ULN (270 Units/L).

CONTINUE FULL DOSE UNLESS ONE OF THE FOLLOWING:

1. Direct bilirubin > 25 μmol/L
2. ALT or AST >20 X ULN (900 Units/L) (GRADE 4 toxicity) on two determinations at least one week apart.

HOLD MTX and monitor weekly labs. Restart at full dose when ALT/AST is <5 X ULN (270 Units/L), and if bilirubin is normal. If dysfunction persists consider a trial period with MTX but without 6MP. Consider liver biopsy and notify treating consultant and study coordinator if both 6MP and MTX cannot be resumed within 2 weeks. Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in ALT or AST > 5 X ULN (270 Units/L).

12.10 Corticosteroids (Dexamethasone or Prednisone)

When dosing dexamethasone during all phases of treatment, adjust the dose upward to the nearest 0.25 for the tablet size. Liquid preparations are also acceptable. Intravenous preparation (6mg/m^2/day) may be used temporarily as needed.

HYPERTENSION: Dose should not be reduced. Medical management of hypertension should be utilized. Avoid calcium channel blockers due to their potential pro-hemorrhagic effect. However, if severe hypertension persists, reduce the dose by 33% until controlled and then resume at full dose.

HYPERGLYCEMIA: Dose should not be reduced. Insulin at appropriate doses and schedule should be used to control blood glucose. Consult endocrinologist for guidance if needed.

PANCREATITIS: Do NOT modify for ASYMPTOMATIC elevations of amylase and/or lipase. DISCONTINUE (except stress doses) for hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and amylase ≥ 2 X ULN (GRADE 3)).

MYOPATHY: Consider measuring CPK with isoenzymes, aldolase, and LDH. Consider EMG studies and referral to physiotherapy. Do not modify dose.

OSTEONECROSIS: DO NOT modify corticosteroid therapy for osteonecrosis during induction or delayed intensification. Consider omitting Maintenance dexamethasone for osteonecrosis GRADE 1 (clinically asymptomatic, radiographic finding only). Omit Maintenance dexamethasone for ≥ GRADE 2 osteonecrosis. Consider resuming Maintenance dexamethasone after 6 months if joint symptoms have resolved and if MRI findings have significantly improved or normalized.

VARICELLA: HOLD during active infection EXCEPT during INDUCTION. Do NOT hold during incubation period following exposure.

INABILITY TO USE ORAL DOSE: Substitute IV mg for mg for dexamethasone.

SEVERE INFECTION: Do NOT hold or discontinue steroids during Induction without serious consideration, as this is a critical period in the treatment of ALL. Later in therapy, one may consider holding steroid until patient achieves cardiovascular stability, except for “stress doses”.

SEVERE PSYCHOSIS: Dose may be discontinued temporarily for severe psychotic episodes, until resolution of symptoms and signs. Dexamethasone can be resumed at a 50% reduction and gradually escalated if there is no recurrence of psychotic symptoms. For mild psychotic changes dose can be reduced by 50%.

INSOMNIA: Sedative may be used for patients with sleep disturbance.

12.11 6-Thioguanine (TG)

CONSOLIDATION: Hold for suspected or proven SERIOUS infection.

NEUTROPENIA and/or THROMBOCYTOPENIA: Do NOT hold TG unless VOD is clinically suspected.

HEPATIC VENO-OCCLUSIVE DISEASE (VOD: This has been observed infrequently. If VOD occurs, WITHHOLD further Ara-C and TG and DO NOT make up doses. All chemotherapy and potentially hepatotoxic drugs should be withheld. Once ascites, thrombocytopenia (< 100) and neutropenia (< 1000) resolve, the subsequent phase of therapy may be started. If VOD occurs in DI#1, substitute it with 6-MP at 60 mg/m^2 for DI#2.

12.12 Vincristine

SIEZURE: Hold 1 dose then reinstitute at full dose. If seizures recur consult neurology.

PERIPHERAL NEUROPATHY: Neuropathy should be documented using the scale provided below.

Modified " Balis" Pediatric Scale of Peripheral Neuropathies	
MOTOR NEUROPATHY	
Grade 1	Subjective weakness, No deficit on neurological exam, other than abnormal deep tendon reflexes
Grade 2	Weakness altering fine motor skills (buttoning shirt, coloring, writing or drawing, eating) or gait abrogating ability to perform tasks.
Grade 3	Unable to perform fine motor tasks or unable to ambulate without assistance.
Grade 4	Paralysis
SENSORY NEUROPATHY	
Grade 1	Paresthesia, pain, or numbness that do not require treatment or interfere with extremity function.

Grade 2	Paresthesia, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills or gait, without abrogating ability to perform tasks.
Grade 3	Paresthesias or pains that are controlled by narcotics, or interfere with extremity function, or quality of life (loss of sleep, normal activities severely impaired).
Grade 4	Complete loss of sensation, or pain that is not controlled by narcotics.

SEVERE NEUROPATHIC PAIN (≥ GRADE 3): Hold dose(s). When symptoms subside resume at 1 mg/m^2, and then escalate to full dose as tolerated. Drugs such as gabapentin may be of value. If severe consider evaluation for Charcot Marie Tooth Disease (CMT), type 1A or hereditary neuropathy with liability to pressure palsies. Ask family history.

VOCAL CORD PARALYSIS: Hold dose(s). When symptoms subside resume at 1mg/ m^2, and then escalate to full dose as tolerated.

FOOT DROP, Paresis: Should be grade 3 to consider holding or decreasing doses. Physical therapy may be beneficial to maintain range of motion and provide AFO's and other forms of support. Gabapentin may be of value.

JAW PAIN – Treat with analgesics, DO NOT modify vincristine dose.

HYPERBILIRUBINEMIA:

Direct bilirubin	**Dose reduction**
<25 μmol/L	Full dose
26-50 μmol/L	50%
51-80 μmol/L	75%
>80 μmol/L	Withhold dose and administer when toxicity resolves

Do NOT make up missed doses

CONSTIPATION OR ILEUS (≥ Grade 3) OR TYPHILITIS: Hold dose(s), institute aggressive regimen to treat constipation if present. When resolve resume at 1 mg/m^2 and escalate to full dose as tolerated.

PTOSIS: Consider pyridoxine and pyridostigmine. Consider dose reduction or holding dose if severe.

EXTRAVASATION:

a. STOP infusion, aspirate drug and blood if possible, remove needle
b. Apply WARM compress immediately for 1 hour then rotate on/off every 15 minutes for 24 hours.
c. Hyaluronidase 150 units/ml reconstituted with NS-inject 1 ml for each 1 ml of drug extravasated or
d. Treat with COLD compresses, dilute through infiltration of 5 ml of an 8.4% solution of sodium bicarbonate and/or local injection of hydrocortisone.

Institutional extravasation guidelines, if available, will supersede the above recommendations.

13.0 Drug Interactions

Since concurrent use of enzyme inducing anticonvulsants (e.g. phenytoin, Phenobarbital, Phenobarbital, and carbamazepine) with antileukemic therapy has recently been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes. Neither Gabapentin nor Levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsant.

Azole antifungals (listed in the table below) and the macrolide group of antibiotics (listed in the table below) may have potent inhibitory effects on drug-metabolizing enzymes, and the doses of some antileukemic drugs (e.g. vincristine and anthracyclines) may need to be reduced in some patients on chronic azole antifungals or antibiotics (see below). **Itraconazole should NOT be used in patients who are receiving vincristine due to a serious drug-drug interaction leading to severe neurotoxicity.**

DRUG	POTENTIAL INTERACTION	ACTION TO BE TAKEN
Anticonvulsants	Induction of drug metabolizing .enzymes Lowered EFS	AVOID phenytoin, Phenobarbital, carbamazepine. Consider Gabapentin or .Levetiracetam as alternative
Rifampin	Induction of drug metabolizing enzymes	DO NOT USE
Azole Antifungals (fluconazole, itraconazole, (voriconazole, ketoconazole	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE

		MEDICATIONS May need dose reductions of vincristine, antracyclines, steroids
Macrolide Antibiotics (erythromycin, clarithromycin, azithromycin, roxithromycin, (telithromycin	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine, anthracyclines, etoposide, steroids

14.0 SUPPORTIVE CARE GUIDELINES

The following guidelines are intended to give general direction for optimal care and to encourage uniformity in the treatment of this population.

14.1 EVALUATION AT DIAGNOSIS

This should be comprehensive and include such diagnostic studies as weight, blood pressure, serum electrolytes, BUN, creatinine, calcium, phosphate, uric acid, prothrombin time, partial thromboplastin time, fibrinogen and appropriate cultures in febrile patients. Details regarding the initial diagnostic workup and evaluation are provided in the Section 2.0.

14.2 HYPERURICEMIA

Hyperuricemia (uric acid > 500 μmol/L) may be present at diagnosis, but more commonly is seen 24-72 hours after initiation of therapy. Uric acid should be monitored before and at least 12, 24, and 48 hours after initiation of therapy. Urine output and blood pressure should be followed q 4 hours and weight at least daily. Early consultation with a nephrologist may be helpful if there is evidence of impending renal failure.

Signs

a) Urate crystals in urine.
b) Hematuria.
c) Decreased urine output.
d) Associated metabolic abnormalities: hyperkalemia, hyperphosphatemia, and hypocalcemia.

Prevention

a) Hydration - 3 L/m²/day to maintain urine output > 100 ml/m²/hour.
b) Alkalization - sodium bicarbonate.

- $NaHCO_3$ 40 mEq/L of IV fluid (120 mEq/m²/day) should be started prior to initiating chemotherapy or 12 gm/m²/day PO prior to initiating chemotherapy to keep urine pH between 6.5 and 8.
- Once chemotherapy has begun, $NaHCO_3$ should be removed from IV solution if hyperphosphatemia is present; too alkaline a urine may predispose to hypoxanthine stones in the presence of allopurinol and calcium/phosphate precipitation in the face of hyperphosphatemia.
- Watch for sodium retention.
- Watch for hyperkalemia.
- Acetazolamide (Diamox) 150 mg/m²/day may be of help in resistant patients, but will exacerbate systemic metabolic acidosis. It is especially useful in patients with simultaneous hyperuricemia and hyperphosphatemia.

c) **Allopurinol** Oral (250-500 mg/m²/day) divided TID (max daily dose 800 mg). Allopurinol can usually be discontinued after 5-7 days.

OR

d**) Rasburicase** The recommended dose and schedule is 0.15 or 0.20 mg/kg as a single daily dose for 5 days. Because the safety and effectiveness of other schedules have not been established, dosing beyond 5 days or administration of more than one course of is not recommended. Chemotherapy should be initiated 4 to 24 hours after the first dose of

rasburicase. **DO NOT ADMINISTER AS A BOLUS INFUSION**, but should be administered as an intravenous infusion over 30 minutes.

Please refer to institutional guidelines for the use of Rasburicase for eligibility and dosing.

Treatment of Tumor Lysis Syndrome (urine output < 60 ml/m²/hour)

a) Mannitol
   1) Test dose 5 gm/m² as 25% solution over 5-10 minutes.
   2) 15 gm/m² q 6 hours to maintain urine output >60 ml/m²/hour.

b) Furosemide 1-3 mg/kg IV q 4-8 hr to maintain output >60 ml/m²/hour.

c) Dialysis: indications when above measures fail.
   1) Hyperkalemia: >6 mEq with rising creatinine if urine output is <60 ml/m²/hour despite Kayexalate, or if there is QRS interval widening on electrocardiogram.
   2) Serum uric acid > 600 µmol/L with rising creatinine and urine output < 60 ml/m²/hour.
   3) Serum creatinine > 2x ULN.
   4) Serum phosphorus > 3 mmol/L or rapidly rising despite aluminum hydroxide with rising creatinine and urine output < 60 ml/m²/hour.
   5) Volume overload.
   6) Symptomatic hypocalcemia with hyperphosphatemia. Hemodialysis or hemoperfusion are generally preferable to peritoneal dialysis in this situation.
   7) Metabolic acidosis with pH less than 7.2, HCO_3 less than 10 mmoL/L.

14.3 BLOOD PRODUCTS

All blood products administered to patients with ALL should be filtered and irradiated.

Red blood cells (RBCs)

RBC transfusion is indicated to correct severe or symptomatic anemia or acute blood loss. If RBC transfusion becomes necessary during maintenance therapy due to severe anemia with reticulocytopenia, physician should consider evaluation for parvovirus with PCR and/or parvovirus IgM titers.

Platelets

Platelet transfusions are indicated for persistent bleeding due to thrombocytopenia, or platelet count < 10,000/µL in patients who have not developed platelet resistance. A platelet count of over 30,000 is required for an LP. Four random donor units/m² (or the equivalent amount as apheresed platelets) should provide a platelet count increment of 40,000/µL. Leukodepletion of platelets is recommended to decrease development of transfusion reactions and transmission of CMV. Some clinicians recommend prophylactic platelet transfusions in any patient with < 20,000/µL platelets, particularly in patients with fever and neutropenia.

Fresh Frozen Plasma

Fresh frozen plasma may be indicated to support coagulation factors in patients with a coagulopathy or hepatic dysfunction.

14.4 INFECTION PROPHYLAXIS

Pneumocystis Carinii
All patients should receive trimethoprim/sulfamethoxazole (TMP-SMX) at a dose of TMP 5 mg/kg/day divided bid on two or three days per week, starting first week of Induction and continuing for 3-4 months post Maintenance therapy.
Patients allergic to or experiencing excessive myelosuppression with TMP-SMX, should be treated with prophylactic oral dapsone (2 mg/kg/day - max 100 mg/24 hours), intravenous pentamidine (4 mg/kg q 2- 4 wks), or aerosolized pentamidine (8 mg/kg for q 4 wks for patients < 5 years of age; 300 mg q 4 wks for children ≥ 5 years of age).Other than TMP/SMX, no routine prophylactic antibacterial agents are to be used.

Fungal Infections
Mycostatin oral swish and swallow (5-10 ml BID) or clotrimazole troches (I BID, suck x 20 min) is recommended for prevention of oral or esophageal candidiasis during treatment with steroids in induction and delayed intensification. In certain situations, oral fluconazole may be appropriate. Use of fluconazole concomitant with thioguanine during delayed intensification, however, should be avoided, if possible.

Gammaglobulin
Some patients develop recurrent sinopulmonary infections in association with low levels of serum IgG while on Maintenance therapy. Monthly replacement therapy with IV IgG (200-400 mg/kg/dose) may be of benefit in such patients.

Varicella Zoster

Varicella Exposure
Determination of varicella immunity status of patients newly diagnosed with leukemia may assist in the future management.
Treatment for Exposed Non-immune Patients
Non-immune patients with significant exposure should be treated with varicella zoster immune globulin (VZIG) 125 units (1 vial) per every 10 kg of body weight (rounded up to a full vial), with a maximum recommended dose of 5 vials (625 Units) by deep intramuscular injection within 72-96 hours of exposure. Scheduled corticosteroid therapy may need to be withheld if lesions develop, but not following exposure during the incubation period. VZIG extends the incubation period from 21 to 28 days or longer.
Varicella Vaccine for Siblings
Non-immune siblings > 1 year old should receive varicella vaccination as soon as possible after diagnosis. In the unlikely event (< 5% chance) that varicella develops in the sibling 10-21 days following vaccination, the patient is unlikely to develop varicella but should receive VZIG.
Varicella Vaccine for Patients
Vaccination with varicella vaccine of patients on treatment for ALL is not encouraged. However, a non-immune patient may receive varicella vaccine (2 injections ~ 2 months apart) during maintenance therapy at the discretion of the individual physician, provided that chemotherapy is not interrupted and the absolute lymphocyte count (WBC/µl x % lymphs) is

≈ 700. A patient who develops rash (≈ 35% incidence) post vaccination may be infectious and should be separated from susceptible patients. A patient who develops rash may benefit from treatment with acyclovir. A post vaccination titer should be obtained 2 months after the second vaccination on treatment, to verify antibody immunity.

Chemotherapy treatment during incubation after VZIG

During incubation (10-28 days after VZIG) the patient should be separated from other compromised hosts. Chemotherapy (including steroids) should not be withheld during incubation but the CBC should be followed to maintain counts within the protocol guidelines.

Treatment of Active Infection

If varicella occurs in a patient on treatment or within 3 months of chemotherapy completion, he/she should be treated with acyclovir 500 mg/m²/dose IV q 8 hours. The usual course is 10 days but it appears that the drug may be stopped when all lesions are scabbed and no new lesions are appearing. Changing from IV to oral acyclovir (3000 mg/m²/day ÷ 4x/day) once no new pox have formed is probably safe practice although published data are lacking.

14.5 FEVER WITH NEUTROPENIA (F & N)

All cases

For patients with ANC < 500/μL and temperature between 38.0°C and 38.5°C twice in 12 hours, or ≥ 38.5°C, empiric parenteral broad spectrum antibiotics should be instituted after obtaining appropriate cultures. It is important to note that fever in patients receiving dexamethasone may be modified (decreased) or even absent when they develop sepsis. Also, patients should be placed on stress doses of corticosteroids if they develop sepsis within few weeks of coming off a prolonged corticosteroid course.

F and N with Myelosuppression

The risk of sepsis is higher during Induction and Delayed Intensification because patients are myelosuppressed and receiving steroids. Fever during these phases warrants examination, CBC, hospital admission, in addition to empiric antibiotics. Duration of therapy should be determined by site of infection (if identified), culture results, and response to treatment.

Persistent F and N

In all cases, if fever and neutropenia persist in the neutropenic patient, systemic antifungal therapy with amphotericin should be initiated after 3-7 days.

In the absence of positive cultures and clinical source of infection, antibiotics should be continued until the patient is afebrile (T < 38.0°C) for at least 24 hours and CBC shows early sings of bone marrow recovery.

Use of Growth Factors

Routine G-CSF should not be administered since neutropenia secondary to chemotherapy as administered on this study is not likely to result in an ANC < 500/μL for a prolonged period of time. The benefit of beginning G-CSF treatment once neutropenia is already present has not been established. G-CSF may be given at an individual investigator's discretion for severe myelosuppression in the face of life-threatening infection.

14.6 NAUSEA AND VOMITING

Antiemetics should be given as needed. The use of high-dose corticosteroids for control of vomiting may influence outcome of this study and is discouraged.

14.7 NUTRITION

An emphasis is placed on maintenance of good nutritional status rather than on correction of the malnourished state. Active measures should be employed to prevent weight loss > 10% of the pre-morbid body weight. Enteral feeding is preferred to parenteral.

14.8 VENOUS ACCESS

Repeated venous access is needed for all patients. Central venous catheters (CVCs) offer reliable access and improved patient comfort at the risk of increased likelihood of infection. Initially, patients with hyperleukocytosis and hyperviscosity may need temporary, percutaneous CVCs inserted without deep sedation or general anesthesia to avoid leukothrombostasis.

14.9 HEPATIC VENO-OCCLUSIVE DISEASE (VOD)

The following studies are recommended for diagnosis and management of VOD secondary to oral TG during Delayed Intensification:

1) CBC
2) Liver function tests: AST, ALT, total and fractionated bilirubin, albumin, alkaline phosphatase.
3) Abdominal ultrasound with doppler evaluation of hepatic and portal venous flow.
4) PT, PTT, fibrinogen, and DIC screen with D-dimer,
5) Hepatitis serology (A, B, C, CMV, EBV).

Serial CBCs and liver function tests are indicated. If weight gain and ascites are present, fluid and salt restriction, furosemide and/or spironolactone should be considered. For hypoalbuminemia and ascites, albumin infusions and furosemide may be of benefit. Thrombocytopenia (presumably secondary to platelet consumption from endothelial damage and chemotherapy-induced myelosuppression) and anemia should be corrected with transfusions to keep platelet count ≥ 20,000/μL. For patients with VOD during Delayed Intensification, platelet transfusions have generally been required for 1 week before platelet counts stabilize. Transaminases have generally risen during the first four days after diagnosis of VOD before declining to normal. Bilirubin levels have often remained normal and rarely been > 65μmol/L. Liver biopsy is not recommended if the diagnosis of VOD can be made by clinical and radiographic criteria, as bleeding can be a serious complication.

14.10 ADDITIONAL GUIDELINES FOR INDUCTION

- Hyperleukocytosis (WBC > 100,000/μL). *Management should be as per institutional/departmental guidelines.*
- Begin allopurinol (300-500 mg/m²/day) or Rasburicase (0.15-0.2 mg/kg) and continue until peripheral blasts and extramedullary disease are reduced.
- Hydrate at 3000 ml/m²/d to maintain urine output > 100 ml/m²/hour beginning approximately 12 hours prior to start of induction therapy and continuing until peripheral blasts and extramedullary disease are reduced.
- Alkalinize urine with $NaHCO_3$ (120 mEq/m²/day) to keep urine pH between 6.5 and 7.0.

- For patients with evidence of coagulopathy of acute leukemia, give fresh frozen plasma at a dose of 10 ml/kg q 6-8 hours initially (or cryoprecipitate).
- Cranial irradiation may be crucial for selected patients.

14.11 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY

- Progressive disease.
- Completion of outlined therapy.
- M2/M3 BM on day 28 of Induction.
- Development of CNS leukemia while receiving therapy.
- Development of M3 BM or extramedullary disease while receiving therapy

14.12 SURGICAL GUIDELINES

Biopsy of the Clinically Enlarged Testis

Testicular biopsy to confirm overt testicular leukemia should be made through the most convenient scrotal incision which overlies the testicular mass and allows minimal scrotal dissection. In the case of overt testicular enlargement, the median raphe is not necessarily the incision of choice because it is necessary to biopsy only the involved testis. The biopsy should be oriented in whichever direction will produce the maximal tumor tissue for the given incision. The specimen should be sufficient for routine histology, electron microscopy, and cell surface marker analysis. A minimum size is probably 3x5 mm.

14.13 RADIATION THERAPY GUIDELINES

General Principles: The radiation therapy described below is standard for the treatment of ALL.

- **Cranial Prophylaxis/Craniospinal Radiation**
  Patients who are slow early responders (SER) receive prophylactic cranial irradiation during consolidation. Patients who are rapid early responders (RER) DO NOT receive prophylactic cranial irradiation.
  All (RER and SER) patients with CNS leukemia (CNS3) at diagnosis will receive craniospinal radiation during Consolidation.
  Patients who develop CNS leukemia while receiving therapy are off protocol therapy.
- **Testicular Radiation**
  All patients with testicular enlargement at diagnosis will receive testicular radiation during Consolidation.

Treatment Regimen

Doses are defined as absorbed dose in cGy to muscle tissue at the prescription point. No correction will be made for tissues inhomogeneity.

Prescription Point

Parallel-Opposed Portals

For equally weighted (balanced) parallel-opposed portals, the prescription point is defined as the point along the central axis of the opposed beams which is between the two entrance points.

Parallel-Opposed, Unequally Weighted or Single Field ("En Face") Beams

The prescription point is defined as a point along the central axis midway in the tumor volume. For these treatments minimum and maximum tumor depths must be ascertained, recorded, and submitted as part of the quality assurance documentation. In addition, the doses to the tumor at minimum and maximum depths
must be calculated and recorded. For patients with central nervous system disease, the spinal cord is considered to be the tumor volume. In this case the prescription point is defined as 4 cm from the posterior skin surface.

Multiple Convergent "Isocentric" Fields

For these complex techniques (e.g., wedged fields, three fields, arc, or rotation), the prescription point is defined as the point which is the intersection of the central axes of these multiple beams (the isocenter).

When these techniques are used, isodose distributions must be calculated and plotted. These are to be submitted as part of the quality assurance documentation. The isocenter must be clearly labeled with the normalization point and dose levels indicated. In addition, an outline of the tumor volume shall be included in the isodose distribution.

Energy

Radiation therapy is to be given with megavoltage sources only: minimum energy 60 Co, maximum energy 6 MV x-rays. Exception: orthovoltage (250:400 KV) or appropriate electron beam may be used for testicular radiation. Minimum acceptable source-to-axis distance (SAD) is 80 cm (except for orthovoltage). Variations from standard SAD/SSD must be reported. All fields should be treated on each day of radiotherapy.

Timing

All treatments will be given on a one fraction per day, 5 day per week fractionation schedule. Fractionation size will vary from 150 to 300 cGy daily as described in the following Sections.

- For all patients, cranial, craniospinal, and/or testicular radiation should begin within 4 days of initiating Phase II Consolidation therapy unless the absolute granulocyte count is less than 750/μL, platelet count is less than 75,000/μL, or there is evidence of sepsis. When treatment is delayed because of a low granulocyte count or low platelet count, radiotherapy should start as soon as the granulocyte count is recovering and has exceeded 750/μL. Patients who have their radiotherapy delayed because of sepsis or suspected sepsis may start treatment as soon as they have been afebrile for 72 hours and are asymptomatic. Patients who develop sepsis during radiotherapy should have radiotherapy stopped.
- If protraction of the course is necessary due to treatment interruption (see above), the total dose, fraction size, and number of fractions should not be altered

Treatment Areas

Cranial Prophylaxis

Patients may be treated supine, prone, or oblique.

Fields

Equally weighted lateral opposed cranial fields including the entire calvarium and brain stem to the level of C2 and upper cervical cord including the C2 vertebral body. The entire subarachnoid space and optic nerves should be included in the fields. The eyes are blocked; however, the block should not extend posterior to the lateral canthus or superior anterior fossa.

Dose

A total dose of 1800 cGy is given in 10 daily fractions of 180 cGy per fraction given Saturday through Wednesday.

Treatment of CNS Leukemia At Diagnosis

Eligibility

All patients who present with CNS leukemia at diagnosis (CNS3, cranial nerve palsies or intracranial parenchymal involvement) will receive craniospinal radiation after successful induction of bone marrow remission.

Patients should be treated in the prone position. If necessary, the cranial portion of the field may be treated with the patient in the oblique or recumbent position providing care is taken not to overlap junction points.

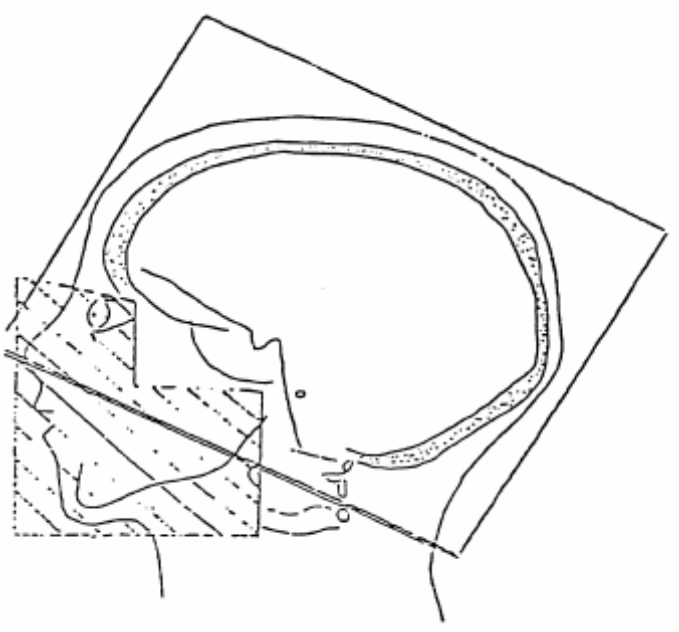


Figure: Cranial Portal (Inferior Border Parallel to Reid's Baseline)

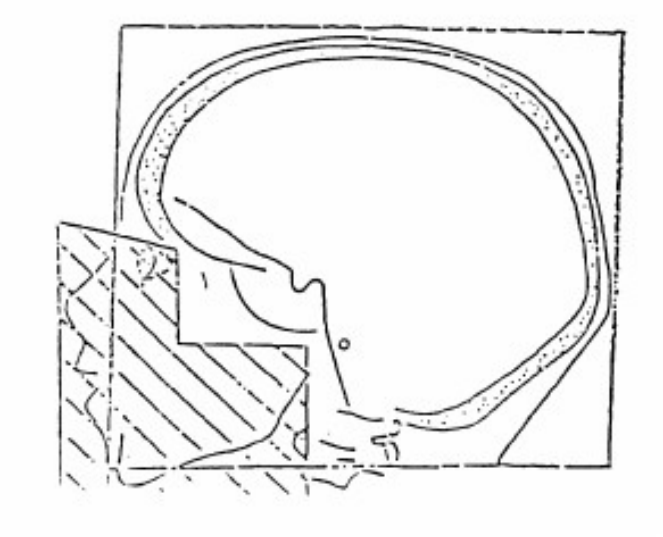


Figure: Cranial Portal (Inferior Border Perpendicular to Long Axis of the Body)

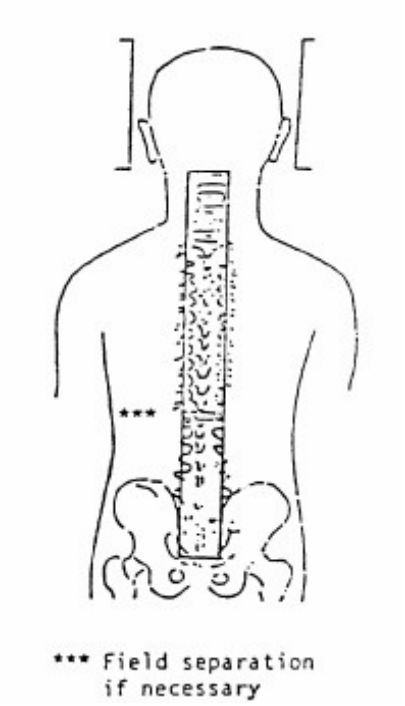
Fields

a) Cranial fields

When the entire spinal axis is going to be treated, the spinal extension of the cranial field may extend to C4-5. (See Figure below)

b) Spinal fields

1. The field shall extend from the lower margin of the cervical extension of the cranial field to include the entire thoracic, lumbar, sacral spine, and coccyx. The field width should cover the entire vertebral body in the cervical, thoracic, and lumbar areas (see Figure) A flare (spade) to cover the sacroiliac joint caudally is not necessary unless the patient has signs of nerve root involvement in this region.
2. The divergent edge of the spinal field should parallel the divergent edge of the inferior margin of the cranial fields. An appropriate separation should be used, and the junction level shifted at least once during treatment.
3. If necessary, the spinal field may be divided into two or more fields with appropriate field separation and junctions shifted at least once during the treatment. The junction level should be placed below L2 if possible.
4. The necessity for multiple fields and the method of field abutment should be determined by the individual physicist and physician. The gaps should be defined and specified on the quality assurance form. Changes in standard SAD/SSD should be reported.



Time-Dose
A total dose of 2400 cGy is delivered to the cranial field in 12 fractions of 200 cGy per fraction given Saturday through Wednesday. A total of 600 cGy is given to the spinal field(s) in daily fractions of 200 cGy per fraction.

Testicular Radiation
Eligibility
Patients with testicular enlargement at diagnosis.
Field
Treatment will be delivered through a single anterior field shielding the penis and encompassing the scrotal skin laterally and inferiorly. The field may be reduced as the palpably enlarged mass decreases in size during treatment.
Time-Dose

1. Both testes are given 2400 cGy in 8 once-daily fractions (300 cGy per fraction) given Saturday through Wednesday. If either testis measures larger than 5 cm at the initiation of radiation, or if testicular enlargement persists after 2400 cGy, the dose to both testes shall be increased to 3000 cGy by giving an additional 600 cGy (300 cGy x 2).
2. The dose is defined at the midplane of the testis. Re-measurement and recalculation should be done if a palpably enlarged testicular mass decreases in size during therapy.

Appendix A

PALL08 Low Risk
Road Map

PHASE I– INDUCTION (WEEKS 4)							
Date Due	**Date Given**	**Day**	**Chemotherapy**				**Labs**
		0	**VCR**		**Pred**	**IT Ara-C**	
		3		**Lasp/P-asp**	**↓**		
		5		**Lasp**	**↓**		
		7	**VCR**	**Lasp**	**↓**		
		10		**Lasp**	**↓**		
		12		**Lasp**	**↓**		
		14	**VCR**	**Lasp**	**↓**	**ITMTX**	**BMA/Bx**
		17		**Lasp**	**↓**		
		19		**Lasp**	**↓**		
		21	**VCR**	**Lasp**	**↓**		
		28			**↓**		**BMA**
					Taper		

Dosages:

Prednisone 40 mg/m^2/ day PO tid x 28 days 0-27,
then taper 20 mg/m^2/d tidx 2 days
and 10 mg/m^2/d bid x 2 days and
then 5mg/m2/day once x 2 days then d/c

Vincristine (VCR) 1.5 mg/m^2 (2mg maximum) IV push

L-Asparaginase (Lasp) 6000 international units/m^2 IM for 9 doses
OR

Peg-asparaginase (P-asp) 2500 international units/ m^2 IM one dose given between days 3 and 5.

Intrathecal cytarabine (ITAraC) 1-2 years: 30 mg;
2-3 years: 50 mg;
> 3 years:: 70 mg.

Itrathecal Methotrexate (ITMTX) 1-2 years: 8 mg;
2-3 years: 10 mg;
> 3 years:: 12 mg.

PALL08 Low Risk
Road Map

PHASE II – CONSOLIDATION (4 WEEKS)							
Date Due	Date Given	Day	Chemotherapy				Labs
		0	VCR	Dex	6MP	ITMTX	
		7		TAPER	6MP	ITMTX	
		14		↓	6MP	ITMTX	
		21			6MP	ITMTX	
		28					

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Dexamethasone (Dex)	**Taper from Induction**
6-Mercaptopurine (6MP)	**75 mg/m^2 PO, in the evening x 28 days**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 Low Risk
Road Map

PHASE III – INTERIM MAINTENANCE (8 WEEKS)							
Date Due	Date Given	Day	Chemotherapy				Labs
		0	VCR	MTX		ITMTX	
		10	VCR	MTX			
		20	VCR	MTX			
		30	VCR	MTX		ITMTX	
		40	VCR	MTX			
		56/0					

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Methotrexate (MTX)	**100 mg/m^2 IV on Day 0; dose should be escalated by 50 mg/m^2 for each subsequent dose (See guidelines in Section 12.8)**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg** **2-3 years: 10 mg** **≥ 3 years: 12 mg**

PALL08 Low Risk
Road Map

PHASE IV – DELAYED INTENSIFICATION; REINDUCTION (4 WEEKS)								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**VCR**	**Doxo**		**DEX**	**IT MTX**	
		3			**Lasp/P-asp**	↓		
		5			**Lasp**	↓		
		7	**VCR**	**Doxo**	**Lasp**			
		10			**Lasp**			
		12			**Lasp**			
		14	**VCR**	**Doxo**	**Lasp**	**DEX**		
		21				↓		
		28				↓		
Road Map continues on next page								

Dosages:

Dexamethasone (DEX)	**10 mg/m^2/day PO on days 0-7 and 14-21; no taper**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Doxorubicin (Doxo)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 3**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg** **2-3 years: 10 mg** **> 3 years: 12 mg**

PALL08 Low Risk
Road Map

PHASE IV – DELAYED INTENSIFICATION; RE-CONSOLIDATION (4 WEEKS)									
Date Due	Date Given	Day	Chemotherapy						Labs
		28	CTX		6TG				
		29		ARAC	↓	IT MTX			
		30		ARAC	↓				
		31		ARAC	↓				
		32		ARAC	↓				
		34			↓				
		35		ARAC	↓	IT MTX			
		36		ARAC	↓				
		37		ARAC	↓				
		38		ARAC	↓				
					↓				
		42			*D/C*		VCR	Lasp/P-asp	
								L-asp	
								L-asp	
		49					VCR	L-asp	
								L-asp	
								L-asp	
		56/0							

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IV over 20 minutes with hydration and Mesna**
6-Thioguanine (6TG)	**60 mg/m^2/d PO X 14 days; days 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 29-32 and 35-38**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
L-asparaginase (LASP)	**6000 international units/m^2 IM X 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM for one dose**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg** **2-3 years: 10 mg** **> 3 years: 12 mg**

PALL08 Low Risk
Road Map

PHASE VII - MAINTENANCE (12 WEEKS COURSES)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	DEX/Pred		6MP	IT MTX	
		7			MTX	↓		
		14			MTX	↓		
		21			MTX	↓		
		28	VCR	DEX/Pred	MTX	↓		
		35			MTX	↓		
		42			MTX	↓		
		49			MTX	↓		
		56	VCR	DEX/Pred	MTX	↓		
		63			MTX	↓		
		70			MTX	↓		
		77			MTX	↓		
		83/0				↓		

Dosages:

Dexamethasone (DEX)	**6 mg/m^2/ day PO in divided doses x 5 days**
Or *for children over 10 years of age*	
Prednisone	**40 mg/m^2/ day PO in divided doses x 5 days**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
6-Mercaptopurine (6MP)	**75 mg/m^2 PO daily**
Methotrexate (MTX)	**20 mg/m^2/ PO weekly**
Methotrexate (MTX) IT	**1-2 years: 8 mg;**
	2-3 years: 10 mg;
	> 3 years: 12 mg

Therapy will end for patients as follows:

1. **Girls will end therapy 2 years from the beginning of Interim Maintenance.**
2. **Boys will end therapy 3 years from the beginning of Interim Maintenance.**
3. **Therapy will end on the anniversary date and the course in progress will <u>NOT</u> be completed.**

Appendix B

PALL08 High Risk
Road Map

PHASE I– INDUCTION (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Dauno		Pred	IT AraC	
		3			Lasp/p-asp	↓		
		5			Lasp	↓		
		7	VCR	Dauno	Lasp	↓		
		10			Lasp	↓		
		12			Lasp	↓		
		14	VCR	Dauno	Lasp	↓	ITMTX	BMA/Bx
		17			Lasp	↓		
		19			Lasp	↓		
		21	VCR	Dauno	Lasp	↓		
		28				Taper	ITMTX	BMA

Dosages:

Prednisone (Pred)	**60 mg/m^2/ day PO x 28 days 0-27, then taper** **30 mg/m^2/d x 3 days** **15 mg/m^2/d x 3 days** **and 7.5 mg/m^2/d x 3 days**
Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
Daunomycin (Dauno)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 9 doses**
OR	
Peg-asparaginase (P-asp)	**2500 international units/ m^2 IM one dose given between days 3 and 5.**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;** **2-3 years: 10 mg;** **> 3 years:: 12 mg.**
IT Cytarabine (ITAraC)	**1-2 years: 30 mg;** **2-3 years: 50 mg;** **> 3 years: 70 mg**

PALL08 High Risk
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**CTX**		**Pred**	**6-MP**	**IT MTX**	CBCd, Chem
		1		**ARAC**	**Pred**	↓		
		2		**ARAC**	**Pred**	↓		
		3		**ARAC**		↓		
		4		**ARAC**		↓		
		6				↓		
		7		**ARAC**		↓	**IT MTX**	CBCd, Chem
		8		**ARAC**		↓		
		9		**ARAC**		↓		
		10		**ARAC**		↓		
		13				↓		
Consolidation Road Map continues in next table								

Dosages:

Prednisone (Pred)	**Tapering doses from induction**
Cyclophosphamide (CTX)	**1000 mg/m^2/ IVPB over 20 minutes, with hydration and Mesna**
6-Mercaptopurine	**60 mg/m^2/d PO X 28 days; days 0-13 and 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 1-4, 7-10, 29-32 and 36-39.**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;** **2-3 years: 10 mg;** **> 3 years: 12 mg**

PALL08 High Risk
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)						
Date Due	**Date Given**	**Day**	***Chemotherapy***			**Labs**
		14	**VCR**	**Lasp/P-asp**	**IT MTX**	CBCd, Chem
		15				
		16		**Lasp**		
		17				
		18		**Lasp**		
		20				
		21	**VCR**	**Lasp**	**IT MTX**	**CBCd, Chem**
		22				
		23		**Lasp**		
		24				
		27		**Lasp**		
Consolidation Road Map continues in next table						

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 14**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;**
	2-3 years: 10 mg;
	> 3 years: 12 mg

PALL08 High Risk
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)						
Date Due	**Date Given**	**Day**	***Chemotherapy***			**Labs**
		28	**CTX**		**6-MP**	CBCd, Chem
		29		**ARAC**	↓	
		30		**ARAC**	↓	
		31		**ARAC**	↓	
		32		**ARAC**	↓	
					↓	
		35		**ARAC**	↓	CBCd, Chem
		36		**ARAC**	↓	
		37		**ARAC**	↓	
		38		**ARAC**	↓	
		41			↓	
Consolidation Road Map continues in next table						

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IVPB over 20 minutes, with hydration and Mesna**
6-Mercaptopurine	**60 mg/m^2/d PO X 28 days; days 0-13 and 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 1-4, 7-10, 29-32 and 35-38.**

PALL08 High Risk
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)					
Date Due	**Date Given**	**Day**	***Chemotherapy***		**Labs**
		42	**VCR**	**Lasp/P-asp**	**CBCd, Chem**
		43			
		44		**Lasp**	
		45			
		46		**Lasp**	
		49	**VCR**	**Lasp**	**CBCd, Chem**
		50			
		51		**Lasp**	
		52			
		53		**Lasp**	

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 42**

PALL08 High Risk
Road Map

PHASE III – INTERIM MAINTENANCE (8 WEEKS)							
Date Due	Date Given	Day	*Chemotherapy*				Labs
		0	VCR	MTX		ITMTX	
		1			LASP/P-asp		
		10	VCR	MTX			
		11			LASP		
		20	VCR	MTX			
		21			LASP/P-asp		
		30	VCR	MTX		ITMTX	
		31			LASP		
		40	VCR	MTX			
		41			LASP		
		56/0					

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Methotrexate (MTX)	**100 mg/m^2 IV on Day 0; dose should be escalated by 50 mg/m^2 for each subsequent dose (See guidelines in Section 12.8)**
L-asparaginase (LASP)	**15000 international units/m^2 IM**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 High Risk
Road Map

PHASE IV – DELAYED INTENSIFICATION; REINDUCTION (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Doxo		DEX	IT MTX	
		3			Lasp/P-asp	↓		
		5			Lasp	↓		
		7	VCR	Doxo	Lasp			
		10			Lasp			
		12			Lasp			
		14	VCR	Doxo	Lasp	DEX		
		21				↓		
		28						
Road Map continues on next page								

Dosages:

Dexamethasone (DEX)	**10 mg/m^2/day PO on days 0-6 and 14-20; no taper**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Doxorubicin (Doxo)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 3**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 High Risk
Road Map

PHASE IV – DELAYED INTENSIFICATION; RE-CONSOLIDATION (4 WEEKS)									
Date Due	**Date Given**	**Day**	***Chemotherapy***						**Labs**
		28	**CTX**		**6TG**				
		29		**ARAC**	**↓**	**IT MTX**			
		30		**ARAC**	**↓**				
		31		**ARAC**	**↓**				
		32		**ARAC**	**↓**				
		34			**↓**				
		35		**ARAC**	**↓**	**IT MTX**			
		36		**ARAC**	**↓**				
		37		**ARAC**	**↓**				
		38		**ARAC**	**↓**				
					↓				
		42			**D/C**		**VCR**	**Lasp/P-asp**	
								L-asp	
								L-asp	
		49					**VCR**	**L-asp**	
								L-asp	
								L-asp	
		56/0							

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IV over 20 minutes with hydration and Mesna**
6-Thioguanine (6TG)	**60 mg/m^2/d PO X 14 days; days 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 29-32 and 35-38**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
L-asparaginase (LASP)	**6000 international units/m^2 IM X 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM for one dose**
Intrathecal Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 High Risk
Road Map

PHASE V - MAINTENANCE (12 WEEKS) COURSE #1 to 4								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**VCR**	**DEX/Pred**		**6MP**	**IT MTX**	
		7			**MTX**	↓		
		14			**MTX**	↓		
		21			**MTX**	↓		
		28	**VCR**	**DEX/Pred**		↓	**IT MTX**	
		35			**MTX**	↓		
		42			**MTX**	↓		
		49			**MTX**	↓		
		56	**VCR**	**DEX/Pred**	**MTX**	↓		
		63			**MTX**	↓		
		70			**MTX**	↓		
		77			**MTX**	↓		
		83/0				↓		

Dosages:

Dexamethasone (DEX) **6 mg/m^2/ day PO in divided doses x 5 days**

Or *for children over 10 years of age*

Prednisone (Pred) **40 mg/m^2/ day PO in divided doses x 5 days**

Vincristine (VCR) **1.5 mg/m^2 (2mg maximum) IV push**

6-Mercaptopurine (6MP) **75 mg/m^2 PO daily**

Methotrexate (MTX) **20 mg/m^2/ PO weekly**

IT Methotrexate (ITMTX) **1-2 years: 8 mg;**
2-3 years: 10 mg;
> 3 years: 12 mg

PALL08 High Risk
Road Map

PHASE V - MAINTENANCE (12 WEEKS) COURSES #5 TO COMPLETION								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**VCR**	**DEX/Pred**		**6MP**	**IT MTX**	
		7			**MTX**	↓		
		14			**MTX**	↓		
		21			**MTX**	↓		
		28	**VCR**	**DEX/Pred**	**MTX**	↓		
		35			**MTX**	↓		
		42			**MTX**	↓		
		49			**MTX**	↓		
		56	**VCR**	**DEX/Pred**	**MTX**	↓		
		63			**MTX**	↓		
		70			**MTX**	↓		
		77			**MTX**	↓		
		83/0				↓		

Dosages:

Dexamethasone (DEX) **6 mg/m^2/ day PO in divided doses x 5 days**
Or *for children over 10 years of age*
Prednisone (Pred) **40 mg/m^2/ day PO in divided doses x 5 days**
Vincristine (VCR) **1.5 mg/m^2 (2mg maximum) IV push**
6-Mercaptopurine (6MP) **75 mg/m^2 PO daily**
Methotrexate (MTX) **20 mg/m^2/ PO weekly**
IT Methotrexate (ITMTX) **1-2 years: 8 mg;**
2-3 years: 10 mg;
> 3 years: 12 mg

Therapy will end for patients as follows:

4. **Girls will end therapy 2 years from the beginning of Interim Maintenance.**
5. **Boys will end therapy 3 years from the beginning of Interim Maintenance.**
6. **Therapy will end on the anniversary date and the course in progress will <u>NOT</u> be completed.**

Appendix C

PALL08 Very High Risk
Road Map

PHASE I– INDUCTION (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Dauno		Pred	IT AraC	
		3			P-asp/Lasp	↓		
		5			Lasp	↓		
		7	VCR	Dauno	Lasp	↓	ITMTX*	
		10			Lasp	↓		
		12			Lasp	↓		
		14	VCR	Dauno	Lasp	↓	ITMTX	BMA/Bx
		17			Lasp	↓		
		19			Lasp	↓		
		21	VCR	Dauno	Lasp	↓	ITMTX*	
		28				Taper	ITMTX	BMA

***Additional doses of ITMTX should be given to patients with CNS 3 disease on Days 7 and 21**

Dosages:

Prednisone (Pred)	**60 mg/m^2/ day PO x 28 days 0-27, then taper 30mg/m^2/d x 3 days 15 mg/m^2/d x 3 days and 7.5 mg/m^2/d x 3 days**
Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
Daunomycin (Dauno)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 9 doses**
OR	
Peg-asparaginase (P-asp)	**2500 international units/ m^2 IM one dose given between days 3 and 5.**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg; 2-3 years: 10 mg; > 3 years:: 12 mg.**
IT Cytarabine (ITAraC)	**1-2 years: 30 mg; 2-3 years: 50 mg; > 3 years: 70 mg**

PALL08 Very High Risk
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	CTX		Pred	6-MP	IT MTX	CBCd, Chem
		1		ARAC	Pred	↓		
		2		ARAC	Pred	↓		
		3		ARAC		↓		
		4		ARAC		↓		
		6				↓		
		7		ARAC		↓	IT MTX	CBCd, Chem
		8		ARAC		↓		
		9		ARAC		↓		
		10		ARAC		↓		
Consolidation Road Map continues in next table								

Dosages:

Prednisone (Pred)	**Tapering doses from induction**
Cyclophosphamide (CTX)	**1000 mg/m^2/ IVPB over 20 minutes, with hydration and Mesna**
6-Mercaptopurine	**60 mg/m^2/d PO X 28 days; days 0-13 and 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 1-4, 7-10, 29-32 and 36-39.**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;** **2-3 years: 10 mg;** **> 3 years: 12 mg**

Patients with CNS 3 disease at diagnosis should receive craniospinal radiation therapy during the Consolidation phase of chemotherapy. Patients with CNS 1 or 2 disease and with SER (Day 14 BM >5% blasts) should receive cranial prophylactic radiation therapy during the Consolidation phase of chemotherapy.
Patients with documented testicular disease at diagnosis should receive testicular radiation therapy during Consolidation phase of chemotherapy.

PALL08 Very High Risk
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)						
Date Due	**Date Given**	**Day**	***Chemotherapy***			**Labs**
		14	**VCR**	**Lasp/P-asp**	**IT MTX**	CBCd, Chem
		15				
		16		**Lasp**		
		17				
		18		**Lasp**		
		20				
		21	**VCR**	**Lasp**	**IT MTX**	**CBCd, Chem**
		22				
		23		**Lasp**		
		24				
		27		**Lasp**		
Consolidation Road Map continues in next table						

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 14**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;**
	2-3 years: 10 mg;
	> 3 years: 12 mg

PALL08 Very High Risk
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)						
Date Due	**Date Given**	**Day**	***Chemotherapy***			**Labs**
		28	**CTX**		**6-MP**	**CBCd, Chem**
		29		**ARAC**	↓	
		30		**ARAC**	↓	
		31		**ARAC**	↓	
		32		**ARAC**	↓	
					↓	
		35		**ARAC**	↓	**CBCd, Chem**
		36		**ARAC**	↓	
		37		**ARAC**	↓	
		38		**ARAC**	↓	
		41			↓	
Consolidation Road Map continues in next table						

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IVPB over 20 minutes, with hydration and Mesna**
6-Mercaptopurine	**60 mg/m^2/d PO X 28 days; days 0-13 and 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 1-4, 7-10, 29-32 and 35-38.**

PALL08 Very High Risk
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)					
Date Due	**Date Given**	**Day**	***Chemotherapy***		**Labs**
		42	**VCR**	**Lasp/P-asp**	**CBCd, Chem**
		43			
		44		**Lasp**	
		45			
		46		**Lasp**	
		49	**VCR**	**Lasp**	**CBCd, Chem**
		50			
		51		**Lasp**	
		52			
		53		**Lasp**	

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 42**

PALL08 Very High Risk
Road Map

PHASE III – INTERIM MAINTENANCE I (8 WEEKS)							
Date Due	Date Given	Day	*Chemotherapy*				Labs
		0	VCR	MTX		ITMTX	
		1			LASP/P-asp		
		10	VCR	MTX			
		11			LASP		
		20	VCR	MTX			
		21			LASP/P-asp		
		30	VCR	MTX		ITMTX	
		31			LASP		
		40	VCR	MTX			
		41			LASP		
		56/0					

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Methotrexate (MTX)	**100 mg/m^2 IV on Day 0; dose should be escalated by 50 mg/m^2 for each subsequent dose (See guidelines in Section 12.8)**
L-asparaginase (LASP)	**15000 international units/m^2 IM**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	≥ 3 years: 12 mg

PALL08 Very High Risk
Road Map

PHASE IV – DELAYED INTENSIFICATION I; REINDUCTION I (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Doxo		DEX	IT MTX	
		3			Lasp/P-asp	↓		
		5			Lasp	↓		
		7	VCR	Doxo	Lasp			
		10			Lasp			
		12			Lasp			
		14	VCR	Doxo	Lasp	DEX		
		21				↓		
		28						
Road Map continues on next page								

Dosages:

Dexamethasone (DEX)	**10 mg/m^2/day PO on days 0-6 and 14-20; no taper**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Doxorubicin (Doxo)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 3**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 Very High Risk
Road Map

PHASE IV – DELAYED INTENSIFICATION I; RE-CONSOLIDATION I (4 WEEKS)									
Date Due	Date Given	Day	*Chemotherapy*						Labs
		28	CTX		6TG				
		29		ARAC	↓	IT MTX			
		30		ARAC	↓				
		31		ARAC	↓				
		32		ARAC	↓				
		34			↓				
		35		ARAC	↓	IT MTX			
		36		ARAC	↓				
		37		ARAC	↓				
		38		ARAC	↓				
					↓				
		42			D/C		VCR	Lasp/P-asp	
								L-asp	
								L-asp	
		49					VCR	L-asp	
								L-asp	
								L-asp	
		56/0							

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IV over 20 minutes with hydration and Mesna**
6-Thioguanine (6TG)	**60 mg/m^2/d PO X 14 days; days 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 29-32 and 35-38**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
L-asparaginase (LASP)	**6000 international units/m^2 IM X 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM for one dose**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 Very High Risk
Road Map

PHASE V – INTERIM MAINTENANCE II (8 WEEKS)							
Date Due	Date Given	Day	*Chemotherapy*				Labs
		0	VCR	MTX		ITMTX	
		1			LASP/P-asp		
		10	VCR	MTX			
		11			LASP		
		20	VCR	MTX			
		21			LASP/P-asp		
		30	VCR	MTX		ITMTX	
		31			LASP		
		40	VCR	MTX			
		41			LASP		
		56/0					

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Methotrexate (MTX)	**100 mg/m^2 IV on Day 0; dose should be escalated by 50 mg/m^2 for each subsequent dose (See guidelines in Section 12.8)**
L-asparaginase (LASP)	**15000 international units/m^2 IM**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 Very High Risk
Road Map

PHASE VI – DELAYED INTENSIFICATION II; REINDUCTION II (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Doxo		DEX	IT MTX	
		3			Lasp/P-asp	↓		
		5			Lasp	↓		
		7	VCR	Doxo	Lasp			
		10			Lasp			
		12			Lasp			
		14	VCR	Doxo	Lasp	DEX		
		21				↓		
		28						
Road Map continues on next page								

Dosages:

Dexamethasone (DEX)	**10 mg/m^2/day PO on days 0-6 and 14-20; no taper**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Doxorubicin (Doxo)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 3**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 Very High Risk
Road Map

PHASE VI – DELAYED INTENSIFICATION II; RE-CONSOLIDATION II (4 WEEKS)									
Date Due	Date Given	Day	*Chemotherapy*						Labs
		28	CTX		6TG				
		29		ARAC	↓	IT MTX			
		30		ARAC	↓				
		31		ARAC	↓				
		32		ARAC	↓				
		34			↓				
		35		ARAC	↓	*IT MTX			
		36		ARAC	↓				
		37		ARAC	↓				
		38		ARAC	↓				
					↓				
		42			D/C		VCR	Lasp/P-asp	
								L-asp	
								L-asp	
		49					VCR	L-asp	
								L-asp	
								L-asp	
		56/0							

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IV over 20 minutes with hydration and Mesna**
6-Thioguanine (6TG)	**60 mg/m^2/d PO X 14 days; days 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 29-32 and 35-38**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
L-asparaginase (LASP)	**6000 international units/m^2 IM X 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM for one dose**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

*** Patients with CNS disease at diagnosis who have received craniospinal radiation therapy will NOT receive IT MTX on Day 35.**

PALL08 Very High Risk
Road Map

PHASE VII - MAINTENANCE

(12 WEEKS)								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**VCR**	**DEX/Pred**		**6MP**	**IT MTX**	
		7			**MTX**	↓		
		14			**MTX**	↓		
		21			**MTX**	↓		
		28	**VCR**	**DEX/Pred**	**MTX**	↓		
		35			**MTX**	↓		
		42			**MTX**	↓		
		49			**MTX**	↓		
		56	**VCR**	**DEX/Pred**	**MTX**	↓		
		63			**MTX**	↓		
		70			**MTX**	↓		
		77			**MTX**	↓		
		83/0				↓		

Dosages:

Dexamethasone (DEX) **6 mg/m^2/ day PO in divided doses x 5 days**

Or *for children over 10 years of age*

Prednisone (Pred) **40 mg/m^2/ day PO in divided doses x 5 days**

Vincristine (VCR) **1.5 mg/m^2 (2mg maximum) IV push**

6-Mercaptopurine (6MP) **75 mg/m^2 PO daily**

Methotrexate (MTX) **20 mg/m^2/ PO weekly**

IT Methotrexate (ITMTX) **1-2 years: 8 mg;**
2-3 years: 10 mg;
> 3 years: 12 mg

Patients on this protocol who have not received any cranial or craniospinal radiation therapy will receive additional doses of intrathecal therapy on Day 28 of each cycle for the first 4 cycles of Maintenance therapy, similar to the PALL08-HR protocol schedule.

Therapy will end for patients as follows:

7. **Girls will end therapy 2 years from the beginning of Interim Maintenance.**
8. **Boys will end therapy 3 years from the beginning of Interim Maintenance.**
9. **Therapy will end on the anniversary date and the course in progress will <u>NOT</u> be completed.**

Appendix D

PALL08-TLR
Road Map

PHASE I– INDUCTION (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Dauno		Pred	IT AraC	
		3			Lasp/p-asp	↓		
		5			Lasp	↓		
		7	VCR	Dauno	Lasp	↓		
		10			Lasp	↓		
		12			Lasp	↓		
		14	VCR	Dauno	Lasp	↓	ITMTX	BMA/Bx
		17			Lasp	↓		
		19			Lasp	↓		
		21	VCR	Dauno	Lasp	↓		
		28				Taper	ITMTX	BMA

Dosages:

Prednisone (Pred)	**60 mg/m^2/ day PO x 28 days 0-27, then taper** **30 mg/m^2/d x 3 days** **15 mg/m^2/d x 3 days** **and 7.5 mg/m^2/d x 3 days**
Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
Daunomycin (Dauno)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 9 doses**
OR	
Peg-asparaginase (P-asp)	**2500 international units/ m^2 IM one dose given between days 3 and 5.**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;** **2-3 years: 10 mg;** **> 3 years:: 12 mg.**
IT Cytarabine (ITAraC)	**1-2 years: 30 mg;** **2-3 years: 50 mg;** **> 3 years: 70 mg**

PALL08-TLR
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**CTX**		**Pred**	**6-MP**	**IT MTX**	CBCd, Chem
		1		**ARAC**	**Pred**	↓		
		2		**ARAC**	**Pred**	↓		
		3		**ARAC**		↓		
		4		**ARAC**		↓		
		6				↓		
		7		**ARAC**		↓	**IT MTX**	CBCd, Chem
		8		**ARAC**		↓		
		9		**ARAC**		↓		
		10		**ARAC**		↓		
		13				↓		
Consolidation Road Map continues in next table								

Dosages:

Prednisone (Pred)	**Tapering doses from induction**
Cyclophosphamide (CTX)	**1000 mg/m^2/ IVPB over 20 minutes, with hydration and Mesna**
6-Mercaptopurine	**60 mg/m^2/d PO X 28 days; days 0-13 and 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 1-4, 7-10, 29-32 and 35-38.**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;** **2-3 years: 10 mg;** **> 3 years: 12 mg**

PALL08-TLR
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)						
Date Due	**Date Given**	**Day**	***Chemotherapy***			**Labs**
		14	**VCR**	**Lasp/P-asp**	**IT MTX**	CBCd, Chem
		15				
		16		**Lasp**		
		17				
		18		**Lasp**		
		20				
		21	**VCR**	**Lasp**	**IT MTX**	**CBCd, Chem**
		22				
		23		**Lasp**		
		24				
		27		**Lasp**		
Consolidation Road Map continues in next table						

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 14**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;**
	2-3 years: 10 mg;
	> 3 years: 12 mg

PALL08-TLR
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)						
Date Due	**Date Given**	**Day**	***Chemotherapy***			**Labs**
		28	**CTX**		**6-MP**	CBCd, Chem
		29		**ARAC**	↓	
		30		**ARAC**	↓	
		31		**ARAC**	↓	
		32		**ARAC**	↓	
					↓	
		35		**ARAC**	↓	CBCd, Chem
		36		**ARAC**	↓	
		37		**ARAC**	↓	
		38		**ARAC**	↓	
		41			↓	
Consolidation Road Map continues in next table						

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IVPB over 20 minutes, with hydration and Mesna**
6-Mercaptopurine	**60 mg/m^2/d PO X 28 days; days 0-13 and 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 1-4, 7-10, 29-32 and 35-38.**

PALL08-TLR
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)					
Date Due	Date Given	Day	*Chemotherapy*		Labs
		42	VCR	Lasp/P-asp	CBCd, Chem
		43			
		44		Lasp	
		45			
		46		Lasp	
		49	VCR	Lasp	CBCd, Chem
		50			
		51		Lasp	
		52			
		53		Lasp	

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 42**

PALL08-TLR
Road Map

PHASE III – INTERIM MAINTENANCE (8 WEEKS)							
Date Due	**Date Given**	**Day**	***Chemotherapy***				**Labs**
		0		**6MP**			
				↓			
		7	**HDMTX**	↓		**ITMTX**	
				↓			
		21	**HDMTX**	↓		**ITMTX**	
				↓			
		35	**HDMTX**	↓		**ITMTX**	
				↓			
		49	**HDMTX**	↓		**ITMTX**	
				↓			
		56		↓			

Dosages:

High Dose Methotrexate (HDMTX)	**5000 mg/m^2 IV over 24 hours (See Section 12.4 for details)**
Mercaptopurine (6MP)	**25 mg/m^2 PO daily for 56 days**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;** **2-3 years: 10 mg;** **> 3 years: 12 mg**

PALL08-TLR
Road Map

PHASE IV – DELAYED INTENSIFICATION; REINDUCTION (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Doxo		DEX	IT MTX	
		3			Lasp/P-asp	↓		
		5			Lasp	↓		
		7	VCR	Doxo	Lasp			
		10			Lasp			
		12			Lasp			
		14	VCR	Doxo	Lasp	DEX		
		21				↓		
		28						
Road Map continues on next page								

Dosages:

Dexamethasone (DEX)	**10 mg/m^2/day PO on days 0-6 and 14-20; no taper**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Doxorubicin (Doxo)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 3**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08-TLR
Road Map

PHASE IV – DELAYED INTENSIFICATION; RE-CONSOLIDATION (4 WEEKS)									
Date Due	**Date Given**	**Day**	***Chemotherapy***						**Labs**
		28	**CTX**		**6TG**				
		29		**ARAC**	↓	**IT MTX**			
		30		**ARAC**	↓				
		31		**ARAC**	↓				
		32		**ARAC**	↓				
		34			↓				
		35		**ARAC**	↓	**IT MTX**			
		36		**ARAC**	↓				
		37		**ARAC**	↓				
		38		**ARAC**	↓				
					↓				
		42			**D/C**		**VCR**	**Lasp/P-asp**	
								L-asp	
								L-asp	
		49					**VCR**	**L-asp**	
								L-asp	
								L-asp	
		56/0							

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IV over 20 minutes with hydration and Mesna**
6-Thioguanine (6TG)	**60 mg/m^2/d PO X 14 days; days 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 29-32 and 35-38**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
L-asparaginase (LASP)	**6000 international units/m^2 IM X 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM for one dose**
Intrathecal Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08-TLR
Road Map

PHASE V - MAINTENANCE (12 WEEKS) COURSE #1 to 4								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**VCR**	**DEX/Pred**		**6MP**	**IT MTX**	
		7			**MTX**	↓		
		14			**MTX**	↓		
		21			**MTX**	↓		
		28	**VCR**	**DEX/Pred**		↓	**IT MTX**	
		35			**MTX**	↓		
		42			**MTX**	↓		
		49			**MTX**	↓		
		56	**VCR**	**DEX/Pred**	**MTX**	↓		
		63			**MTX**	↓		
		70			**MTX**	↓		
		77			**MTX**	↓		
		83/0				↓		

Dosages:

Dexamethasone (DEX) **6 mg/m^2/ day PO in divided doses x 5 days**

Or *for children over 10 years of age*

Prednisone (Pred) **40 mg/m^2/ day PO in divided doses x 5 days**

Vincristine (VCR) **1.5 mg/m^2 (2mg maximum) IV push**

6-Mercaptopurine (6MP) **75 mg/m^2 PO daily**

Methotrexate (MTX) **20 mg/m^2/ PO weekly**

IT Methotrexate (ITMTX) **1-2 years: 8 mg;**
2-3 years: 10 mg;
> 3 years: 12 mg

PALL08-TLR
Road Map

PHASE V - MAINTENANCE (12 WEEKS) COURSES #5 TO COMPLETION								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**VCR**	**DEX/Pred**		**6MP**	**IT MTX**	
		7			**MTX**	↓		
		14			**MTX**	↓		
		21			**MTX**	↓		
		28	**VCR**	**DEX/Pred**	**MTX**	↓		
		35			**MTX**	↓		
		42			**MTX**	↓		
		49			**MTX**	↓		
		56	**VCR**	**DEX/Pred**	**MTX**	↓		
		63			**MTX**	↓		
		70			**MTX**	↓		
		77			**MTX**	↓		
		83/0				↓		

Dosages:

Dexamethasone (DEX)	**6 mg/m^2/ day PO in divided doses x 5 days**
Or *for children over 10 years of age*	
Prednisone (Pred)	**40 mg/m^2/ day PO in divided doses x 5 days**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
6-Mercaptopurine (6MP)	**75 mg/m^2 PO daily**
Methotrexate (MTX)	**20 mg/m^2/ PO weekly**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;**
	2-3 years: 10 mg;
	> 3 years: 12 mg

Therapy will end for patients as follows:

10. **Girls will end therapy 2 years from the beginning of Interim Maintenance.**
11. **Boys will end therapy 3 years from the beginning of Interim Maintenance.**
12. **Therapy will end on the anniversary date and the course in progress will <u>NOT</u> be completed.**

Appendix E

PALL08 THR
Road Map

PHASE I– INDUCTION (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Dauno		Pred	IT AraC	
		3			Lasp/p-asp	↓		
		5			Lasp	↓		
		7	VCR	Dauno	Lasp	↓	ITMTX*	
		10			Lasp	↓		
		12			Lasp	↓		
		14	VCR	Dauno	Lasp	↓	ITMTX	BMA/Bx
		17			Lasp	↓		
		19			Lasp	↓		
		21	VCR	Dauno	Lasp	↓	ITMTX*	
		28				Taper	ITMTX	BMA

***Additional doses of ITMTX should be given to patients with CNS 3 disease on Days 7 and 21**

Dosages:

Prednisone (Pred)	**60 mg/m^2/ day PO x 28 days 0-27, then taper 30mg/m^2/d x 3 days 15 mg/m^2/d x 3 days and 7.5 mg/m^2/d x 3 days**
Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
Daunomycin (Dauno)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 9 doses**
OR	
Peg-asparaginase (P-asp)	**2500 international units/ m^2 IM one dose given between days 3 and 5.**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg; 2-3 years: 10 mg; > 3 years:: 12 mg.**
IT Cytarabine (ITAraC)	**1-2 years: 30 mg; 2-3 years: 50 mg; > 3 years: 70 mg**

PALL08 THR
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**CTX**		**Pred**	**6-MP**	**IT MTX**	**CBCd, Chem**
		1		**ARAC**	**Pred**	↓		
		2		**ARAC**	**Pred**	↓		
		3		**ARAC**		↓		
		4		**ARAC**		↓		
		6				↓		
		7		**ARAC**		↓	**IT MTX**	**CBCd, Chem**
		8		**ARAC**		↓		
		9		**ARAC**		↓		
		10		**ARAC**		↓		
		13				↓		
Consolidation Road Map continues in next table								

Dosages:

Prednisone (Pred)	**Tapering doses from induction**
Cyclophosphamide (CTX)	**1000 mg/m^2/ IVPB over 20 minutes, with hydration and Mesna**
6-Mercaptopurine	**60 mg/m^2/d PO X 28 days; days 0-13 and 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 1-4, 7-10, 29-32 and 35-38.**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;** **2-3 years: 10 mg;** **> 3 years: 12 mg**

PALL08 THR
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)						
Date Due	**Date Given**	**Day**	***Chemotherapy***			**Labs**
		14	**VCR**	**Lasp/P-asp**	**IT MTX**	CBCd, Chem
		15				
		16		**Lasp**		
		17				
		18		**Lasp**		
		20				
		21	**VCR**	**Lasp**	**IT MTX**	**CBCd, Chem**
		22				
		23		**Lasp**		
		24				
		27		**Lasp**		
Consolidation Road Map continues in next table						

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 14**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;**
	2-3 years: 10 mg;
	> 3 years: 12 mg

PALL08 THR
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)						
Date Due	**Date Given**	**Day**	***Chemotherapy***			**Labs**
		28	**CTX**		**6-MP**	**CBCd, Chem**
		29		**ARAC**	↓	
		30		**ARAC**	↓	
		31		**ARAC**	↓	
		32		**ARAC**	↓	
					↓	
		36		**ARAC**	↓	**CBCd, Chem**
		37		**ARAC**	↓	
		38		**ARAC**	↓	
		39		**ARAC**	↓	
		41			↓	
Consolidation Road Map continues in next table						

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IVPB over 20 minutes, with hydration and Mesna**
6-Mercaptopurine	**60 mg/m^2/d PO X 28 days; days 0-13 and 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 1-4, 7-10, 29-32 and 35-38.**

PALL08 THR
Road Map

PHASE II – CONSOLIDATION (9 WEEKS)					
Date Due	**Date Given**	**Day**	***Chemotherapy***		**Labs**
		42	**VCR**	**Lasp/P-asp**	**CBCd, Chem**
		43			
		44		**Lasp**	
		45			
		46		**Lasp**	
		49	**VCR**	**Lasp**	**CBCd, Chem**
		50			
		51		**Lasp**	
		52			
		53		**Lasp**	

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2.0 mg maximum) IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 42**

PALL08 THR
Road Map

PHASE III – INTERIM MAINTENANCE I (8 WEEKS)							
Date Due	**Date Given**	**Day**	***Chemotherapy***				**Labs**
		0		**6MP**			
				↓			
		7	**HDMTX**	↓		**ITMTX**	
				↓			
		21	**HDMTX**	↓		**ITMTX**	
				↓			
		35	**HDMTX**	↓		**ITMTX**	
				↓			
		49	**HDMTX**	↓		**ITMTX**	
				↓			
		56		↓			

Dosages:

High Dose Methotrexate (HDMTX)	**5000 mg/m^2 IV over 24 hours (See Section 12.4 for details)**
Mercaptopurine (6MP)	**25 mg/m^2 PO daily for 56 days**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg;** **2-3 years: 10 mg;** **> 3 years: 12 mg**

PALL08 THR
Road Map

PHASE IV – DELAYED INTENSIFICATION I; REINDUCTION I (4 WEEKS)								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**VCR**	**Doxo**		**DEX**	**IT MTX**	
		3			**Lasp/P-asp**	↓		
		5			**Lasp**	↓		
		7	**VCR**	**Doxo**	**Lasp**			
		10			**Lasp**			
		12			**Lasp**			
		14	**VCR**	**Doxo**	**Lasp**	**DEX**		
		21				↓		
		28						
Road Map continues on next page								

Dosages:

Dexamethasone (DEX)	**10 mg/m^2/day PO on days 0-6 and 14-20; no taper**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Doxorubicin (Doxo)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 3**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 THR
Road Map

PHASE IV – DELAYED INTENSIFICATION I; RE-CONSOLIDATION I (4 WEEKS)									
Date Due	Date Given	Day	*Chemotherapy*						Labs
		28	CTX		6TG				
		29		ARAC	↓	IT MTX			
		30		ARAC	↓				
		31		ARAC	↓				
		32		ARAC	↓				
		34			↓				
		35		ARAC	↓	IT MTX			
		36		ARAC	↓				
		37		ARAC	↓				
		38		ARAC	↓				
		42			D/C		VCR	Lasp/P-asp	
								L-asp	
								L-asp	
		49					VCR	L-asp	
								L-asp	
								L-asp	
		56/0							

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IV over 20 minutes with hydration and Mesna**
6-Thioguanine (6TG)	**60 mg/m^2/d PO X 14 days; days 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 29-32 and 35-38**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
L-asparaginase (LASP)	**6000 international units/m^2 IM X 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM for one dose**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 THR
Road Map

PHASE V – INTERIM MAINTENANCE II (8 WEEKS)							
Date Due	Date Given	Day	*Chemotherapy*				Labs
		0	VCR	MTX		ITMTX	
		1			LASP/P-asp		
		10	VCR	MTX			
		11			LASP		
		20	VCR	MTX			
		21			LASP/P-asp		
		30	VCR	MTX		ITMTX	
		31			LASP		
		40	VCR	MTX			
		41			LASP		
		56/0					

Dosages:

Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Methotrexate (MTX)	**100 mg/m^2 IV on Day 0; dose should be escalated by 50 mg/m^2 for each subsequent dose (See guidelines in Section 12.3)**
L-asparaginase (LASP)	**15000 international units/m^2 IM**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg** **2-3 years: 10 mg** **> 3 years: 12 mg**

PALL08 THR
Road Map

PHASE VI – DELAYED INTENSIFICATION II; REINDUCTION II (4 WEEKS)								
Date Due	Date Given	Day	*Chemotherapy*					Labs
		0	VCR	Doxo		DEX	IT MTX	
		3			Lasp/P-asp	↓		
		5			Lasp	↓		
		7	VCR	Doxo	Lasp			
		10			Lasp			
		12			Lasp			
		14	VCR	Doxo	Lasp	DEX		
		21				↓		
		28						
Road Map continues on next page								

Dosages:

Dexamethasone (DEX)	**10 mg/m^2/day PO on days 0-6 and 14-20; no taper**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
Doxorubicin (Doxo)	**25 mg/m^2 IV push**
L-Asparaginase (Lasp)	**6000 international units/m^2 IM for 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM on Day 3**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 THR
Road Map

PHASE VI – DELAYED INTENSIFICATION II; RE-CONSOLIDATION II (4 WEEKS)									
Date Due	Date Given	Day	*Chemotherapy*						Labs
		28	CTX		6TG				
		29		ARAC	↓	IT MTX			
		30		ARAC	↓				
		31		ARAC	↓				
		32		ARAC	↓				
		34			↓				
		35		ARAC	↓	*IT MTX			
		36		ARAC	↓				
		37		ARAC	↓				
		38		ARAC	↓				
		42			D/C		VCR	Lasp/P-asp	
								L-asp	
								L-asp	
		49					VCR	L-asp	
								L-asp	
								L-asp	
		56/0							

Dosages:

Cyclophosphamide (CTX)	**1000 mg/m^2/ IV over 20 minutes with hydration and Mesna**
6-Thioguanine (6TG)	**60 mg/m^2/d PO X 14 days; days 28-41**
Cytosine Arabinoside (ARAC)	**75 mg/m^2/day IV push on days 29-32 and 35-38**
Vincristine (VCR)	**1.5 mg/m^2 (2mg maximum) IV push**
L-asparaginase (LASP)	**6000 international units/m^2 IM X 6 doses**
OR	
Pegylated Asparaginase (P-asp)	**2500 international units/m^2 IM for one dose**
IT Methotrexate (ITMTX)	**1-2 years: 8 mg**
	2-3 years: 10 mg
	> 3 years: 12 mg

PALL08 THR
Road Map

PHASE VII - MAINTENANCE (12 WEEKS)								
Date Due	**Date Given**	**Day**	***Chemotherapy***					**Labs**
		0	**VCR**	**DEX/Pred**		**6MP**	**IT MTX**	
		7			**MTX**	↓		
		14			**MTX**	↓		
		21			**MTX**	↓		
		28	**VCR**	**DEX/Pred**	**MTX**	↓		
		35			**MTX**	↓		
		42			**MTX**	↓		
		49			**MTX**	↓		
		56	**VCR**	**DEX/Pred**	**MTX**	↓		
		63			**MTX**	↓		
		70			**MTX**	↓		
		77			**MTX**	↓		
		83/0				↓		

Patients with CNS 3 disease at diagnosis should receive craniospinal radiation therapy during the first course of maintenance chemotherapy. Patients with CNS 1 or 2 disease should receive cranial prophylactic radiation therapy during the first course of maintenance.

Dosages:

Dexamethasone (DEX) **6 mg/m^2/ day PO in divided doses x 5 days**

Or *for children over 10 years of age*

Prednisone (Pred) **40 mg/m^2/ day PO in divided doses x 5 days**

Vincristine (VCR) **1.5 mg/m^2 (2mg maximum) IV push**

6-Mercaptopurine (6MP) **75 mg/m^2 PO daily**

Methotrexate (MTX) **20 mg/m^2/ PO weekly**

IT Methotrexate (ITMTX) **1-2 years: 8 mg;**
2-3 years: 10 mg;
> 3 years: 12 mg

Patients on this protocol who have not received any cranial or craniospinal radiation therapy will receive additional doses of intrathecal therapy on Day 28 of each cycle for the first 4 cycles of Maintenance therapy, similar to the PALL08-HR protocol schedule.

Therapy will end for patients as follows:

13. **Girls will end therapy 2 years from the beginning of Interim Maintenance.**
14. **Boys will end therapy 3 years from the beginning of Interim Maintenance.**

15. **Therapy will end on the anniversary date and the course in progress will <u>NOT</u> be completed.**