THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Augmented Berlin-Frankfurt-Munster therapy for adolescents/young adults with acute lymphoblastic leukemia or lymphoblastic lymphoma
2006-0375

Core Protocol Information

Short Title	Augmented BFM therapy for your adolescent /young adults with acute lymphoblastic leukemia or acute lymphoblastic lymphoma
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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

Primary objective:

1.1 To assess the feasibility and the effectiveness of pediatric type therapy (augmented BFM) in patients age 12 through 30 with untreated precursor-B or T acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL).

Secondary

1.1.2 To evaluate the prognostic significance of minimal residual disease in bone marrow samples at the end of induction and at the end of consolidation in this group of patients.

1.1.3 To prospectively evaluate gene hypermethylation status in this group of patients.

1.1.4 To prospectively analyze asparaginase activity and anti-asparaginase antibody formation in this population of patients.

2.0 Background

2.1 Pediatric ALL Trials

Pediatric patients with ALL historically have been grouped into high and standard risk categories according to age and presenting white blood cell count (WBC). Patients over age 10, patients with a presenting WBC >50,000, and patients with T-lineage disease are regarded as high risk patients. Prior to 1981, this group had an EFS of approximately 40%. Recently, Children's Cancer Group study CCG-1961 has shown an improvement in EFS to over 80% in high risk patients who respond rapidly to initial treatment (1). This treatment, known as augmented BFM therapy, uses intensified therapy with increased asparaginase and vincristine as well as escalating methotrexate therapy during the interim maintenance phase (consolidation 3 in this protocol) of chemotherapy.

2.2 Adult ALL Trials

Prognosis in adult ALL is influenced by age, performance status, and organ function as well as presenting WBC. In addition, high risk cytogenetic abnormalities such as the Philadelphia chromosome are more likely to be present in adults with ALL than in pediatric patients (2). More favorable prognostic features such as high hyperdiploidy and the presence of the TEL-AML translocation are found less often in adult ALL patients than in pediatric patients (3). Survival rates in adult ALL patients continues to lag behind that seen in pediatric patients at least partly due to these findings, with long term EFS in adult ALL and LL patients ranging from 40-50% (4,5,6).

2.3 Adolescents and Young Adults with ALL on Pediatric or Adult Trials

Patients between the ages of 15 and 21 years of age with ALL may be treated on pediatric treatment regimens or adult treatment regimens depending on referral

patterns. In retrospective reviews comparing survival in this age group treated often in very disparate fashions, pediatric regimens have produced survival rates superior to adult treatment regimens in this age group (3,7,8). Further analysis of two large adult series report that the survival rates for patients age 21 through 29 are essentially the same as that seen in patients age less than 21 (3,5). In these retrospective comparisons, patient characteristics in the pediatric trials and in the adult trials have been very similar. The most obvious difference between the two groups of patients is therapy; pediatric regimens in general use higher doses of vincristine, asparaginase and methotrexate than adult regimens.

Recently, the results of the Children's Cancer Group trial, CCG-1961, were analyzed specifically for patients age 16 to 21 (1). These patients were treated with so called "augmented BFM" therapy with a single phase of delayed intensification if they were in remission by day 14 of therapy. The event free survival (EFS) rate at five years was 81.3% and the overall survival (OS) rate at five years was 84.2% for rapid early responders treated with augmented therapy. Patients who were not in remission by day 14 were treated with augmented therapy and received two blocks of delayed intensification and two blocks of interim maintenance therapy before proceeding on to maintenance chemotherapy. The results for CCG-1961 are comparable to the survival rates obtained in other pediatric group trials for high-risk patients, including teen-aged patients (9,10,11,12). We propose to use the same therapy as used for patients aged 16-21 on CCG-1961 in adult patients with ALL age 12 to 35. If pediatric-type therapy is the cause for the improved survival rates seen for teens and young adults in pediatric trials, then similar improvements might be expected in patients aged 18 to 21 treated at MDACC using this regimen, and improved survival rates in patients aged 22 to 30 could perhaps also be realized.

An obvious question will be whether older adults will have excess toxicity using this regimen, but this seems unlikely. Older adults are currently treated with the Hyper CVAD regimen, a regimen that uses intensively timed blocks of high dose corticosteroids, cytarabine, adriamycin, methotrexate, and cyclophosphamide as well as standard doses of vincristine. In addition, the current adult regimen uses a very similar maintenance phase as that in pediatric trials. Toxicity has not been reported to be excessive in adults treated with this regimen (6). The University of California-Los Angeles and the Dana Farber Cancer Institute are attempting to give pediatric based ALL therapy to adults, with the DFCI study including patients up to age 50. So far, excessive toxicity has not limited therapy at these centers.

2.4 Lymphoblastic Lymphoma (LL)

The vast majority of lymphoblastic lymphomas are of T-cell phenotype. T cell-lymphoblastic leukemia and T-cell lymphoblastic lymphoma are indistinguishable in terms of malignant cell morphology, histology and phenotype. The pediatric approach to therapy is very similar to that used in ALL with the exception that the duration of therapy for LL is shorter (13). In general, the long-term survival results for adults with LL "fall short" of the result seen in children with LL (14). Hyper CVAD therapy used in patients with lymphoblastic lymphoma has produced a DFS of 66% (15). In general,

however, reported survival rates for adults with LL are approximately 45-50%, as seen in ALL. The long-term event free survival rates in children with lymphoblastic lymphoma reported by pediatric groups have generally been around 75% (16,17). Recently published results using BFM therapy, similar to that proposed in this trial, show a five-year event free survival for T-LL that is 90% (15). Similarly, Cairo et al. reported that therapy similar to the augmented BFM treatment used in pediatric ALL is effective in LL, with long-term overall survival of 85%-90% in localized disease and 65-85% in advanced disease (18).Since the results have been excellent using BFM-type therapy for LL, and since this is the proposed therapy for patients on this study, young adult patients with LL will also be enrolled on this study. Some differences in therapy between LL patients and ALL patient will be maintained: 1) stage I and II patients will not receive maintenance intrathecal therapy and 2) total treatment duration will be two years for all the LL patients.

2.4.1 Radiation and LL

Locoregional radiation therapy to the mediastinum has been shown to reduce local failures in adult patients with LL(19, 20). Pediatric LL patients treated with current intensive chemotherapy regimens do not show any benefit from local radiation (21). Since the chemotherapy regimen is duplicating that used in teens and young adults by the Children's Cancer Group, radiation therapy will not be used routinely to the mediastinum. In the event of persistent, active disease at day 35 either by PET scan or biopsy, then surgical removal of disease is performed followed by continued chemotherapy. This approach has been utilized by the German pediatric oncology group with excellent results (15).

2.6 Minimal Residual Disease (MRD)

MRD status during therapy has been reported to highly predict prognosis in pediatric ALL using both molecular or flow-cytometric methods for disease detection (22,23,24,25). These studies and others all clearly indicate that low MRD levels, especially measured early during therapy, indicate a favorable prognosis. Data on the presence of MRD at the end of induction and during therapy shows a similar prognostic value in adult patients (26,27) Current studies in the COG are assessing the prognostic and therapeutic value of MRD in both ALL and LL. A secondary objective of this trial will be to collect data on the presence of MRD and its prognostic significance in young adults treated with pediatric type therapy.

2.7 Hypermethylation

Promoter gene hypermethylation is found in virtually every type of cancer and is associated with transcriptional silencing of genes. Aberrant methylation is a mechanism of gene inactivation in tumors and is at least as common as more classic mechanisms of tumor suppressor gene disruption such as translocation (28). Recently, promoter gene hypermethylation has been reported to be a prognostic factor in ALL (28, 29). Increased gene methylation is a plausible explanation for the decreased survival seen in

young adults with ALL compared to children. An aim of this study will be to accumulate further data on gene hypermethylation in young adults with ALL.

2.8 Asparaginase

Asparaginase is an important component in the therapy of acute lymphoblastic leukemia and of lymphoblastic lymphoma in children. The asparaginases deplete asparagine in leukemic cells which results in leukemic cell death (30). PEG-asparaginase, a long-acting formulation of asparaginase appears to be at least as effective in depleting asparagine as other forms of asparaginase and may be less immunogenic (31, 32). This is important since the formation of anti-asparaginase antibodies results in low levels of asparaginase activity and may neutralize the effect of the asparaginases (33). While clinical studies have reported on antibody formation and asparagine levels in children, little data is available for the adult population. An aim of this study will be to examine asparaginase activity and anti-asparaginase antibody formation in the young adults treated on this protocol.

3.0 Clinical Pharmacology

4.0 Background Drug Information

1. PEG Asparaginase (Pegaspargase, Oncaspar)

THERAPEUTIC CATEGORY
Antineoplastic Agent; Enzyme

FORMULATION
Supplied in preservation-free isotonic sterile solution ready for injection containing 750 IU/mL (3750 IU/vial). No reconstitution necessary.

STABILITY AND STORAGE
Keep refrigerated. Do not freeze. Do not use if cloudy or if precipitate is present. Avoid excessive agitation. DO NOT SHAKE. Keep refrigerated. Do not use if stored at room temperature for more than 48 hours. Do not use if product has been frozen.

MECHANISM OF ACTION
Pegaspargase is a modified version of asparaginase. Leukemic cells, especially lymphoblasts, require exogenous asparagine; normal cells can synthesize asparagine. Asparaginase contains L-asparaginase amidohydrolase type EC-2 which inhibits protein synthesis by deaminating asparagine to aspartic acid and ammonia in the plasma and extracellular fluid and therefore deprives tumor cells of the amino acid for protein synthesis. Asparaginase is cycle-specific for the G_1 phase of the cell cycle.

TOXICITIES
Systemic anaphylactoid reactions, and local allergic reactions. Pancreatitis.

Hyperglycemia with glucosuria. Hypoalbuminemia, hypofibrinogenemia, and hypercoagulable state.

STATUS
Commercially available

2. Cyclophosphamide (Cytoxan, Neosar)
THERAPEUTIC CATEGORY
Alkylating Agent; Antineoplastic Agent; Nitrogen Mustard

FORMULATION
Supplied as Intravenous Powder for Solution: 100 mg, 200 mg, 500 mg, 1 g, and 2 g of Cytoxan per vial or Tablets of 25 mg and 50 mg.

RECONSTITUTION
For IV: reconstitute each vial with Sterile or Bacteriostatic Water for Injection, USP, to a final concentration of 20 mg/ml. No data is available concerning compatibility with KC1 or NaHCO3.

STABILITY AND STORAGE REQUIREMENTS
Reconstituted solution is stable for 24 hours at room temperature, or 6 days if refrigerated. Solution reconstituted without preservation should be discarded after 6 hours.

MECHANISM OF ACTION
Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

TOXICITIES
Myelosuppression. Anorexia, nausea and vomiting. Alopecia. Hemorrhagic cystitis, and bladder fibrosis. Acute congestive heart failure. Syndrome of inappropriate antidiuretic hormone (SIADH). Oligospermia or a zoospermia, amenorrhea, sterility. A small but potential risk of developing secondary AML.

STATUS
Commercially available

3. Cytosine Arabinoside (Ara-C, Cytarabine, Cytosar-U)
THERAPEUTIC CATEGORY
Antimetabolite Antineoplastic; Antineoplastic Agent; Pyrimidine Analog

FORMULATION
Supplied as lyophilized powder, 100 mg, 500 mg, 1 g, and 2 g of Ara-C per vial.

RECONSTITUTION
For IM, IV push, and SQ: reconstitute each vial with enclosed diluent as recommended. For high dose IV Ara-C infusion, do not use enclosed diluent; use NS without preservative. For IT: reconstitute with preservative free Lactated Ringer's, or Normal Saline. Ara-C is compatible with KC1 and NaHCO3.

STABILITY AND STORAGE
Reconstituted solution is stable for 48 hours at room temperature. Solution reconstituted without preservative should be discarded after 8 hours. Discard solution if light haze develops. Store at room temperature

MECHANISM OF ACTION
Inhibition of DNA synthesis. Cytosine gains entry into cells by a carrier process, and then must be converted to its active compound, aracytidine triphosphate. Cytosine is a purine analog and is incorporated into DNA; however, the primary action is inhibition of DNA polymerase resulting in decreased DNA synthesis and repair. The degree of cytotoxicity correlates linearly with incorporation into DNA; therefore, incorporation into the DNA is responsible for drug activity and toxicity. Cytarabine is specific for the S phase of the cell cycle.

TOXICITIES
Myelosuppression. Anorexia, nausea and vomiting, diarrhea, and mucosal ulceration. Transient liver function abnormalities. Alopecia. "Ara-C syndrome: "fever, myalgia, bone pain, occasional chest pain, maculopapular rash, conjunctivitis, malaise. After high doses: confusion, somnolence, seizures, ataxia, and slurred speech.

STATUS
Commercially available

4. <u>Daunomycin Hydrochloride (Cerubidine®, Daunorubicin Hydrochloride)</u>
THERAPEUTIC CATEGORY
Anthracycline; Antineoplastic Agent; Antitumor Antibiotic

FORMULATION
Supplied as lyophilized powder in 20 mg vials
RECONSTITUTION
Reconstitute with 4 ml of Sterile Water for Injection. Agitate gently until the material has completely dissolved.
Avoid extravasation or severe local tissue necrosis may result.

STABILITY AND STORAGE
Stable for 24 hours at room temperature and 48 hours under refrigeration. Protect from exposure to sunlight. store product at 15 – 25º C.

MECHANISM OF ACTION

Inhibition of DNA and RNA synthesis by intercalation between DNA base pairs and by steric obstruction. Daunomycin intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA

TOXICITIES
Locally necrotizing if extravasated, alopecia, nausea and vomiting, bone marrow depression, serious myocardial toxicity may be seen as the total dose approaches 550 mg/m2.

STATUS
Commercially available

5 Dexamethasone (Decadron®)
THERAPEUTIC CATEGORY
Adrenal Corticosteroid; Antiemetic; Corticosteroid, Nasal; Corticosteroid, Ophthalmic; Corticosteroid, Topical

FORMULATION
Supplied as tablets of 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg and 6 mg and Injection solution with 4 mg/ml or 24 mg/ml.

RECONSTITUTION
Premixed

STABILITY AND STORAGE
Note expiration date on vial or bottle. Store in room temperature. Protect vials from light.

MECHANISM OF ACTION
Decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown

TOXICITIES
Salt or fluid retention, hypertension, potassium loss. Muscle weakness, loss of muscle mass, severe arthralgia, aseptic necrowsis of femoral humeral heads, osteoporosis. Peptic ulcer, Pancreatitis, abdominal distention, ulcerative esophagitis. Impaired wound healing, thin fragile skin, striae, bruises, facial erythema. Convulsion, headache, increased intracranial pressure. Cushingoid state, suppression of growth in children. Posterior subcapsular cataracts, increased intraocular pressure. Fatigue, psychosomatic complaints.

STATUS

Commercially available.

6. Doxorubicin (Adriamycin)

THERAPEUTIC CATEGORY

Anthracycline; Antineoplastic Agent; Antitumor Antibiotic Formulation

FORMULATION

Supplied as lyophilized red-orange powder: 10 mg, 20 mg, 50 mg, and 150 mg of Adriamycin per vial, or 10 mg/5 ml, 20 mg/10 ml, 50 mg/25 ml, and 20 mg/100 ml liquid reconstituted single-use vials.

RECONSTITUTION

For powder vials: use NS without preservatives to attain a concentration of 2 mg/ml (add 5 ml to 10 mg vial; 10 ml to 20 mg vial; 25 mg ml to 50 mg vial; 75 ml to 150 mg vial). Single-use liquid vials are already in solution. No data is available concerning compatibility with KCl or NaHCO3.

STABILITY AND STORAGE

Reconstituted powder vials are stable for 24 hours at room temperature and 48 hours under refrigeration and protected from light. The reconstituted single-use vials have no preservative, but are stable for 24 hours at room temperature.Store at room temperature protected from light, for powder vials. Refrigerate liquid vials and protect from light.

MECHANISM OF ACTION

Inhibition of DNA and RNA synthesis by intercalation between DNA base pairs by inhibition of topoisomerase II and by steric obstruction. Doxorubicin intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA. Doxorubicin is also a powerful iron chelator; the iron-doxorubicin complex can bind DNA and cell membranes and produce free radicals that immediately cleave the DNA and cell membranes

TOXICITIES

Myelosuppression. Anorexia, mucositis, nausea and vomiting. Alopecia, hyperpigmentation of nail beds and dermal creases may occur. Several soft tissue damage with extravasation. Transient liver function abnormalities. Drug-induced congestive heart failure when the cumulative dose exceeds 450 mg/m2.

STATUS

Commercially available.

7. 6-Mercaptopurine (6-MP, Purinethol®)

THERAPEUTIC CATEGORY

Antimetabolite Antineoplastic; Antineoplastic Agent; Purine Analog

FORMULATION

Supplied in 50 mg tablets.

STORAGE

Store at room temperature.

MECHANISM OF ACTION

Purine antagonist which inhibits DNA and RNA synthesis; acts as false metabolite and is incorporated into DNA and RNA, eventually inhibiting their synthesis; specific for the S phase of the cell cycle

TOXICITIES

Myelosuppression. Nausea and vomiting, diarrhea. Hepatocellular or obstructive liver disease. Mild atopic dermatitis.

8. Methotrexate(MTX, Amethopterin)

THERAPEUTIC CATEGORY

Antifolate; Antimetabolite Antineoplastic; Antineoplastic Agent; Folate Antagonist

FORMULATION

Oral – 2.5 mg tablets. Lyophilized powder, 20 mg, 50 mg, 100 mg, 200 mg and 1 gm per vial. Liquid with preservative, 25 mg/ml, 2 ml (50 mg) and 10 ml (250 mg) per vial. Liquid without preservative, 50 mg, 100 mg, 200 mg, 250 mg per vial.

RECONSTITUTION

Reconstitute powder vials with sterile water, NS or D5W. Reconstitute the 20 mg and 50 mg vials to a concentration no greater than 25 mg/ml. The 1 gm vial should be reconstituted with 19.4 ml NS or D5W to a concentration of 50 mg/ml. Further dilution with D5W or NS is acceptable. No data is available fro KC1 compatibility, but is compatible with NaHCO3. For IT use, mix Methotrexate WITHOUT PRESERVATIVE with preservative-free Lactated Ringer's or Normal Saline.

STABILITY AND STORAGE

Reconstituted solutions without preservatives should be discarded after 8 hours. Solutions with preservative stored at room temperature maintain 90% of label potency. Store at room temperature. Protect from light.

MECHANISM OF ACTION

Methotrexate is a folate antimetabolite that inhibits DNA synthesis. Methotrexate irreversibly binds to dihydrofolate reductase, inhibiting the formation of reduced folates, and thymidylate synthetase, resulting in inhibition of purine and thymidylic acid synthesis. Methotrexate is cell cycle specific for the S phase of the cycle.

TOXICITIES

Myelosuppression. Anorexia, stomatitis, nausea and vomiting. Transient liver function abnormalities. Alopecia, rashes, photosensitivity, depigmentation or hyperpigmentation of skin. Drowsiness, blurred vision, leukoencephalopathy, paresis. Interstitial pneumonitis. Osteoporosis. Fever. Defective zoogenesis, or spermatogenesis, transient oligospermia, menstrual dysfunction and infertility.

STATUS
Commercially available.

9. Prednisone
THERAPEUTIC CATEGORY
Adrenal Corticosteroid
FORMULATION
Supplied as tablets of 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 50 mg. Oral solution with 5 mg/ml.
STORAGE
Room temperature.

MECHANISM OF ACTION
Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system; suppresses adrenal function at high doses. Antitumor effects may be related to inhibition of glucose transport, phosphorylation, or induction of cell death in immature lymphocytes. Antiemetic effects are thought to occur due to blockade of cerebral innervation of the emetic center via inhibition of prostaglandin synthesis.

TOXICITIES
Salt or fluid retention, hypertension, potassium loss. Muscle weakness, loss of muscle mass, severe arthralgia, aseptic necrosis of femoral/humeral heads, osteoporosis. Peptic ulcer, Pancreatitis, abdominal distention, ulcerative esophagitis. Impaired wound healing, thin fragile skin, striae, bruises, facial erythema. Convulsions, headache, increased intracranial pressure. Cushingoid state, suppression of growth in children. Posterior subcapsular cataracts, increased intraocular pressure. Fatigue, psychosomatic complaints.

STATUS
Commercially available.

10. 6-Thioguanine (6-TG)
THERAPEUTIC CATEGORY
Antimetabolite Antineoplastic; Antineoplastic Agent; Purine Analog

FORMULATION
Supplied as tablets of 40 mg.

STORAGE
Store at room temperature.

MECHANISM OF ACTION
Purine analog that is incorporated into DNA and RNA resulting in the blockage of synthesis and metabolism of purine nucleotides

TOXICITIES
Myelosuppression. Nausea and vomiting, anorexia, stomatitis, diarrhea.
Veno-occulusive disease. Increased skin sensitivity to sun, mild atopic dermatitis. Loss of vibration sensitivity and unsteady gait.

STATUS
Commercially available.

11. Vincristine (Oncovin®)
THERAPEUTIC CATEGORY
Antineoplastic Agent; Vinca Alkaloid

FORMULATION
Supplied as clear liquid, 1 mg 2 mg, and 5 mg vials.

STABILITY AND STORAGE
Keep refrigerated. Protect from light. Multiple-dose containers with preservatives are stable 30 days after opening if refrigerated.

MECHANISM OF ACTION
Binds to tubulin and inhibits microtubule formation; therefore arresting the cell at metaphase by disrupting the formation of the mitotic spindle; it is specific for the M and S phases. Vincristine may also interfere with nucleic acid and protein synthesis by blocking glutamic acid utilization

TOXICITIES
Neuromuscular effects, jaw pain, constipation, loss of deep tendon reflexes, foot and wrist drop, paresthesia, alopecia, convulsion (rare). Alopecia. Hyponatremia (SIADH). Severe soft tissue damage if extravasated.

STATUS
Commercially available.

5.0 Patient Eligibility

5.1 Inclusion Criteria

1. Patients must have precursor-B or T-lymphoblastic leukemia or lymphoblastic lymphoma.

2. Patients must be untreated or have had only one prior chemotherapy regimen for ALL or LL . Previously treated patients will be analyzed separately.

3. Age between 12 to 40 years old

4. Patients with CNS disease or testicular disease are eligible.

5. Intrathecal therapy with cytarabine is allowed prior to registration for patient convenience. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. Systemic chemotherapy must begin within 72 hours of the first intrathecal treatment.

6. Signed informed consent prior to the start of systemic therapy. In the event of enrollment of a minor patient, an attempt to obtain assent from the patient must be documented, and parental consent must be signed.

7. Echocardiogram should be done within 72 hours of starting therapy if there are cardiac risk factors (e.g., history of hypertension or of myocardial infarction)

8. Creatinine should be < 3 mg/dL bilirubin < 3 mg/dl unless felt to be due to disease

9. Zubrod Performance status of <3

10. Patients who received steroids more than 72 hours prior to study enrollment are eligible but will be analyzed separately.

5.2 Exclusion Criteria

1. Age less than twelve years of age or greater than 40 years.

2. More than one prior treatment regimen for ALL or LL.

3. The patient is pregnant or unwilling to practice appropriate birth control.

4. Presence of the Philadelphia chromosome t(9;22)

6.0 Evaluation During Study

6.1 Pre-treatment

History and physical examination with bone marrow aspirate and biopsy (optional). Further testing is as per standard new leukemia patient evaluation.

Echocardiogram should be done within 7 days hours of starting therapy if there are cardiac risk factors (e.g., history of hypertension or of myocardial infarction)

For patients with lymphoblastic lymphoma:
Lymphoma patients will have standard imaging as per new lymphoblastic lymphoma patients.

6.2 During Treatment

6.2.1 Induction: Bone marrow evaluation at day 15 +/- 2days and bone marrow aspiration at day 29+/- 2 days for morphology and minimal residual disease testing.

Extended Induction: A bone marrow aspiration is required after 2 weeks of extended induction.

6.2.2 Consolidation 1
A bone marrow aspiration is performed at the end of consolidation 1 for morphology and minimal residual disease testing.

6.3 During Maintenance
Once the patient has entered maintenance, they should be monitored for event free survival.

7.0 Treatment Plan

All patients must begin therapy with an intrathecal treatment using cytarabine 100 mg. Induction chemotherapy must begin within 3 days of the intrathecal cytarabine dose.

Patients with less than or equal to 5% blasts in the bone marrow by day 15 will be considered rapid early responders (RER) and will receive augmented BFM therapy with single delayed intensification and will continue treatment with consolidation 1, 2 and 3 parts A and B followed by maintenance therapy .

Patients with more than 5% blasts in the bone marrow after two weeks of induction therapy will be considered slow early responders (SER) and will receive augmented BFM with double delayed intensification. Patients with > 5% blasts and <25% blasts in the bone marrow after induction will receive 2 weeks of extended Induction therapy. If the patient has a bone marrow showing remission by week 6, patient will continue treatment with two courses of consolidation 2 and two courses of consolidation 3 parts A and B before proceeding to maintenance therapy. Patients who do not have a bone marrow remission after 6 weeks of therapy will be taken off protocol.

Parameters to begin next phase of therapy include absolute neutrophil count of >750 L K/UL and platelets >75 K/UL.

In Consolidation 1, pause therapy at day 29 (week 5) until the absolute neutrophil count is >750 and platelets are >75 K/microliter.

For all vincristine dose, If body surface area (BSA) is less than 1.3 m2 then the dose will be calculated using BSA with a maximum dose of 2 mg.

Treatment assignment
CNS therapy: If the CSF is positive for blasts at the start of therapy, then the following intrathecal schedule is to be followed: Methotrexate 12 mg IT weekly until negative for

blasts, then Methotrexate 12 mg IT every other week for 8 doses, then Methotrexate 12 mg IT monthly for 6 doses. If CSF is negative for blasts at the start of therapy, then follow IT methotrexate schedule indicated for each cycle.

CNS 3: Augmented BFM therapy with double delayed intensification and additional radiation therapy will be as per attending physician's discretion following discussion with the study principal investigator

Testicular involvement: Augmented BFM with double delayed intensification and additional radiation therapy will be as per attending physician's discretion following discussion with the study principal investigator

LL: Augmented BFM with a single delayed intensification; treatment length of 24 months

LL with CNS involvement: Augmented BFM with a single delayed intensification and cranial radiation during consolidation as per attending physician's discretion following discussion with the study principal investigator

7.1 Induction (4 weeks)

Daunorubicin 25 mg/m2 IV weekly x 4 doses.
Vincristine 2 mg IV weekly x 4 doses.
Prednisone 60 mg/m2/day, maximum dose of 120 mg/day in divided doses (BID or TID) PO on days 1-28.
PEG-asparaginase 2000 international units (IU)/m2 (maximum dose 3750 IU) IV in week 1.
Intrathecal Methotrexate 12 mg on week 2 and week 5.

7.1.2 Extended Induction (2 weeks)

Daunorubicin 25mg/m2 IV in week 5
Vincristine 2 mg IV on weeks 5 and 6
Prednisone 60 mg/m2/day, maximum dose of 120 mg/day in divided PO daily in weeks 5 and 6
PEG-asparaginase 2000 IU/m2 (maximum dose 3750 IU) IV in week 5.

7.2 Consolidation 1 (8 weeks)

Cyclophosphamide 1 g/m2 IV in weeks1 and 5.
Cytarabine 75 mg/m2 SC or IV on days 1-4 and days 8-11 of both months.
Mercaptopurine 60 mg/m2/d PO on days 1-14 of each month.
Vincristine 2 mg IV in week 3 and 4 of each month.
PEG-asparaginase 2000 IU/m2 (maximum dose 3750 IU) IVIV in weeks 3 and 6.
Intrathecal Methotrexate 12 mg weekly for the first month only.

7.3 Consolidation 2 (7 weeks)

Vincristine 2 mg IV every 10 days +/- 2 days for 5 doses.
Methotrexate IV over 15 minutes, starting at 100mg/m2 and escalating by 50 mg/m2/dose every 10 +/- 2 days for 5 doses to toxicity (e.g myelosuppression or mucositis grade 3).
PEG-asparaginase 2000 IU/m2 (maximum dose 3750 IU) IV in week 1 and week 4.
Intrathecal Methotrexate 12 mg week 1 and week 5.

7.4 Consolidation 3- Part A (4 weeks)

Vincristine 2 mg IV in weeks 1, 2 and 3
Dexamethasone 10 mg/m2/d PO in divided doses on days 1-7 and days 15-21
Doxorubicin 25 mg/m2 IV in weeks 1, 2 and 3.
PEG-asparaginase 2000 IU/m2 (maximum dose 3750 IU) IV in week 1
Intrathecal Methotrexate 12 mg in week 1.

7.5 Consolidation 3- Part B (4 weeks)

Cyclophosphamide 1 g/m2 IV in week 1.
Cytarabine 75 mg/m2 SQ or IV for four consecutive days in weeks 1 and 2
Thioguanine 60 mg/m2 days PO daily for two weeks
Intrathecal Methotrexate 12 mg in weeks 1 and 2
Vincristine 2mg IV on weeks 3 and 4
PEG-Asparaginase 2000 IU/m2 (maximum dose 3750 IU) on week 3

NOTE: Slow early responders repeat consolidation 2 and consolidation 3, A and B, prior to maintenance chemotherapy.

7.6 Maintenance for patients with ALL (24 months)

Vincristine 2 mg IV every month.
Dexamethasone 6 mg/m2/d in divided doses PO for 5 days every month
Mercaptopurine 75 mg/m2/d PO daily.
Methotrexate 20 mg/m2 PO every week.
Intrathecal methotrexate 12 mg every 3 months for the first 12 months of maintenance.

7.7 Maintenance for patients with LL (maintenance stops two years from the start of chemotherapy)

Vincristine 2 mg IV every month.
Dexamethasone 6 mg/m2/d in divided doses PO for five days every month.
Mercaptopurine 75 mg/m2/d PO daily.
Methotrexate 20 mg/m2 PO every week.

8.0 Supportive Care

Patients should start Bactrim prophylaxis for Pneumocystis by week 2 of induction. During induction and delayed intensification, additional prophylactic anti-bacterial, anti-viral and anti-fungal therapies are at the discretion of the attending physician.

Prophylactic antibiotics may be given with each course until neutrophil recovery 500/microliter or greater and will vary according to the patient's tolerance and allergies.

Suggested medications for supportive care include:

Levaquin 500 mg daily (or other quinolone) or trimethoprim/sulfamethoxazole double strength b.i.d. on Monday-Wednesday and Friday.
Fluconazole 200 mg daily or itraconazole 200 mg b.i.d. or other appropriate antifungal agent
Valacyclovir 500 mg daily or acyclovir 200 mg b.i.d. or other appropriate antiviral agent

For metabolic support, induction therapy should include intravenous alkalinization and hyperhydration along with oral allopurinol. Uricozyme may be substituted for allopurinol at the investigators discretion

9.0 Dose Modifications for Toxicities

Intrathecal Cytarabine (Day 0 of Induction)
Do not hold dose.

1. Steroid
Steroids should not be held for hypertension unless the hypertension is severe. In cases of severe hypertension, reduce the dose by 33%. Steroids should not be altered for diabetes or pancreatitis. For psychosis, administer half the dose. If myopathy develops, measure the serum CPK and consider EMG studies. Omit further steroids if avascular necrosis develops. Steroids should be held during active varicella zoster infection except during induction.

2. Vincristine
Hold one dose for seizures. Hold doses for severe foot drop, paresis, abdominal pains, obstipation or ileus. Resume at one-half the dose when symptoms improve and escalate to full dose as tolerated. If the total bilirubin is greater than 2 mg/dL, then fractionate the bilirubin. If the direct bilirubin is greater than 1 mg/dL, then hold vincristine. Also hold vincristine if the AST/ALT is greater than 1000 U/l on two evaluations at least one week apart or if the PT is prolonged above normal.

3. PEG-Asparaginase
Discontinue for systemic allergic reaction to PEG-asparaginase. Discontinue in the presence of pancreatitis documented by an elevated serum amylase or lipase or

ultrasound abnormalities. Do not re-start if there is a prior history of asparagninase induced pancreatitis. Do not modify the dose for hyperglycemia. Hold if there is ketonemia not controlled by insulin. Hold for significant thrombosis until the thrombus resolves. Coagulopathy without bleeding is not an indication to withhold asparaginase. Replace fibrinogen with cryoprecipitate and replace AT III with fresh frozen plasma. For transaminases >200, obtain a total bilirubin. Hold asparaginase if the total bilirubin is >1.9 mg/dL. Administer half the dose if the total bilirubin is 1.5-1.9 mg/dL. Erwinia chrysanthemi L-aparaginase (Erwinase) may be used as a substitute in case of systemic allergic reaction to Peg-Asparaginase. Follow manufacturer's recommendation on dosage and timing of administration. Consult Principal Investigator prior to ordering the drug.

4. Daunomycin
Do not administer if there is congestive heart failure. Hold if the total bilirubin is > 7 mg/dL; if 5-7, give 6.25 mg/m2; if 3-5, give 12.5 mg/m2; if < 3 mg/dL, give the whole dose. The third or fourth dose may be delayed or omitted for severe infection or mucositis. Upon recovery, full doses are given.

5. Intrathecal Methotrexate
Do not reduce the dose for systemic toxicity. Leucovorin may be used as a single 10 mg/m2 dose to reduce the risk of already existent myelosuppression (ANC < 500/ microliter) and mucositis. Do not use leucovorin for myelosuppression alone. For seizures, paresis or organic brain syndrome attributed to methotrexate, omit methotrexate intrathecally and substitute cytarabine.

6. Oral Methotrexate
a. Neutropenia and thrombocytopenia: ANC < 1000 and > 750
Do not modify the dose, but recheck the CBC in one week. If the CBC shows an ANC <1000 and > 750, continue at full dose. Hold doses if the ANC <500/microliter and re-start at 50% dose when the ANC > 1000/microliter.

b. ANC < 750 and > 500
Reduce the dose by 50%. Re-check the CBC weekly and increase in 25% increments to full dose when the ANC recovers to greater than 1000.
Platelets < 100k and >75k, modify as for ANC <1000/microliter and >750/microliter.
Platelets <75k and >50k, modify as for ANC <750/microliter and >500/microliter.
Platelets <50k, modify as for ANC < 500/microliter.

c. Severe diarrhea or persistent vomiting.
Discontinue methotrexate. Re-start at 50% of the original dose and escalate as clinically appropriate. Reduce the dose to 50% if grade 3 mucositis develops. Hold the methotrexate if grade 4 mucositis develops and restart at 50% of the prior dose with gradual dose escalation.

d. Liver dysfunction
Obtain a total bilirubin if the transaminase (GPT or GOT) is greater than 200 U/L.

Monitor the GPT or GOT along with the bilirubin every 2 weeks during consolidation and every 4 weeks during maintenance. Continue full dose therapy unless the bilirubin is greater than 2 mg/dL or the GPT or GOT is over 1000 U/L on two determination at least 2 weeks apart. If either of these occur, hold the methotrexate and monitor labs weekly. Re-start at full dose when the transaminase is less than 200 U/L if the bilirubin is normal.

e. Nephrotoxicity
For grade 2-4 nephrotoxicity, omit the methotrexate until the problem has resolved (grade 0).

7. IV Methotrexate
a. Liver Dysfunction
Omit until grade 0-2 toxicity, then re-start at half dose. Escalate by 25% at two week intervals if grade 3-4 toxicity does not recur.

b. Kidney Dysfunction
Hold IV methotrexate until toxicity has resolved (grade 0). Resume at 100% dose.

c. Mucositis
Decrease the dose by 30% for grade 2 mucositis that persists for 3 days. Hold the drug for grade 3-4 stomatitis and resume at 50% with subsequent escalations by 25% to full dose.

d. Neutropenia
During the escalation of IV methotrexate, only methotrexate should be held for ANC<750/microliter or platelets <75K. Upon recovery of the ANC>750 and platelets >75K, the next methotrexate dose should be reduced by 20%. If there is no recovery of the ANC or platelet count despite holding two doses of IV methotrexate, Please contact study PI and schedule a bone marrow aspiration.

8. Mercaptopurine
Do not modify in consolidation for low counts.

a. Neutropenia and thrombocytopenia
Do not change the dose for ANC >750 or platetets > 75,000. For an ANC >500 but <750, reduce by 50% until ANC > 1000 and the platelets >75,000. Escalate the dose by 25% to full dose as peripheral blood counts allow.

b. For an ANC <500 or platelets <50,000,
Discontinue the drug and resume when the ANC >1000 and the platelets >75,000. Escalate the mercaptopurine by 25% in weekly intervals as the peripheral blood counts allow.

c. Liver Dysfunction
Same as for oral methotrexate.

d. Mucositis Same as for oral methotrexate.

9. Doxorubicin
The drug is contraindicated in congestive heart failure.
a. Hyperbilirubinemia
Same as for Daunorubicin.

b. Neutropenia
The 3rd dose of doxorubicin in consolidation 3A may be omitted for fever and presumed severe infection or for severe mucositis preventing oral intake (grade 3-4). The subsequent dose should be given at full dose. If the delay exceeds one week, notify the PI and do not give the 3rd dose. Therapy with cyclophosphamide will begin on day 28 provided blood count criteria are met.

10. Cyclophosphamide
a. Gross hematuria or prior microscopic hematuria
Hydrate for 24 hours after the dose and use MESNA 360 mg/m2 pre, hour 4, 7 and 11.

b. SIADH
Manage with saline and lasix.

d. Therapy with cyclophosphamide will begin on day 28 provided blood count criteria ANC >750 and platelets > 75,000/microliter are met.

11. Cytarabine
a. Cytarabine syndrome
Do not hold the dose for fever if the fever is likely due to cytarabine. For rash or conjunctivitis grade 3-4, hold the drug until the toxicity resolves.

b. Liver Dysfunction
Same as for oral methotrexate. Re-start when the transaminase is less than 200 U/L and the bilirubin is normal .

12. Thioguanine
Do not modify the dose for low blood counts.

a. Liver Dysfunction
Monitor GPT or GOT and total bilirubin before each 4 day course of cytarabine while the patient is receiving thioguanine. Modify as per oral methotrexate guidelines.

13. Escalation of Mercaptopurine (MP) and Methotrexate (MTX) during Maintenance Therapy
The oral doses of MP and MTX should be adjusted to maintain the ANC between

750/microliter and 1500/microliter and the platelet count >75,000/microliter.

a. If the ANC is > 1500/microliter on Day 0 of any maintenance course, and the ANC was > 1500/microliter on days ~~)~~, 28 and 56 of the preceding maintenance course, then the MP dose should be increased by 25%. Subsequently, if the monthly ANC is:1) >750 and <1500, then make no change

b. If the ANC is <750 and >500 or platelets <75,000, then reduce the MP dose to 50% of the original dose and increase the MP dose by 25% to full dose when the ANC>750~~,~~ ~~3)~~

c. If the ANC is >1500 and platelets >75,000, then increase the methotrexate dose by 25%. Continue to increase the MP dose at day 0 of each maintenance course as above it the ANC persists >1500/microliter. There is no maximum dose for the MP or oral MTX.

10.0 Reporting Requirements

10.1 Adverse Events

Expected events related to the study are described in section 3, in appendix A guidelines for reporting adverse events (ADR's) to the Institutional Review Board (IRB) and in appendix E leukemia guidelines for Adverse events reporting.These events will be scored using the NCI toxicity scoring system in appendix B

10.2 Reporting Requirements
Serious and unexpected adverse events occuring during the treatment phase up to 30 days post treatment will be reported accordingly to MD Anderson guidelines

11.0 Criteria for Response

11.1 Complete Remission- ALL and LL
For ALL, an absolute neutrophil count greater than 1000/mm3 and platelet count >100k/mm3 and bone marrow with 5% or less blasts. Resolution of extramedullary disease is required for complete remission.
For LL, complete response is complete disappearance of all lesions by physical exam, by imaging studies and in the bone marrow or CNS (if involved at the onset of therapy). Or, in the event of persistent masses, the largest tumors must show >55% decrease in the products of the two greatest perpendicular diameters of up to 6 of the largest masses. In addition, the PET scan must be negative to designate a CR.

11.2 Partial Remission
For ALL, as above with 6-25% marrow blasts.
For LL, greater than a 30% decrease in the products of the greatest perpendicular masses of up to six of the largest tumors but not satisfying the criteria for CR. Any morphologic evidence of CNS or marrow disease must resolve.

11.3 CNS Leukemia

CNS leukemia will be defined as >/= 5 WBC/microliter and a cytocentrifuge specimen showing leukemic blasts. CNS leukemia may also be diagnosed if the CSF WBC is normal but clinical signs of CNS involvement are present.

11.3.1 If there are leukemia cells in the peripheral blood and the lumbar puncture is traumatic with >/= 5 WBC/microliter, then the following algorithm is used: if CSF WBC/ CSF RBC >Blood WBC/Blood RBC, then the patient has CNS leukemia.

11.4 Testicular Leukemia
Unilateral or bilateral testiculomegaly. Biopsy is required if the physical exam is equivocal.

11.5 Bone Marrow Status
M1: Less than 5% blasts on bone marrow differential.
M2: 5-25% blasts on bone marrow differential.
M3: >25% blasts on bone marrow differential.

11.6 Rapid Early Responder (RER)
Day 14 bone marrow with </= 5% blasts

11.6 Slow Early Responder (SER)
Day 14 bone marrow with > 5% blasts

11.7 Unfavorable Characteristics
a Philadelphia chromosome present. These patients are not eligible for this protocol.
b t(4;11) present
c. Hypodiploidy (</= 44 chromosomes)

Patients with hypodiploidy should be strongly considered for transplant.
Patients with the t(4;11) should be strongly considered for transplant.

12.0 Criteria for Removal from the Study

1. Progressive disease
2. M3 marrow at day 28 of induction.
3. Development of CNS leukemia while receiving therapy.
4. Bone marrow, extramedullary or testicular relapse while receiving therapy
5. Unfavorable characteristics are diagnosed.
6.Unacceptable toxicity; grade 4, life threatening toxicities that preclude administration of essential chemotherapy.
7. Patient or guardian requests removal from study.
8. Development of a second malignancy.
9. Physician determines that it is in the patient's best interest to be removed from therapy.
10. For patients requiring extended induction, those who do not have </= 5% blasts in the bone marrow at the end of 6 weeks of therapy.

11. Failure to acheive a CR in LL patients by the end of consolidation 1 therapy. (histological confirmation of disease, if feasible, is strongly recommended).
12. Upon completion of the study treatment, patients are not required to return for follow-up care. Patients should be encouraged to return for a yearly evaluation.
13. Patients will be followed for survival after the completion of therapy even if clinical documentation is difficult to obtain from outside offices.

13.0 Number of Patients

Statistical Considerations:

This is a single-arm, open-label, phase II trial. The primary objective of this trial is to assess the efficacy and toxicity of the augmented Berlin-Frankfurt-Munich (BFM) chemotherapy regimen in untreated acute lymphoblastic leukemia (ALL) patients of age 12 through 30. The primary end point is 3-year event-free survival (EFS) rate. Current practice in the study population yields a 3-year EFS rate of 40-50% with response (defined as CR after four weeks of treatment) rate of 90%. The toxicity rate of standard induction is 33% when one looks at grade 3-4 infection. The study regimen will be considered successful if it exhibits a 3-year EFS rate greater than 60% and response rate no less than 90% with Grade III-IV infectious toxicity rate in induction no more than 33%. A maximum of 125 patients will be enrolled with accrual rate of 2-3/month, thus we estimate this study will be completed in six years.

Sample Size and End Point Monitoring:

The 3-year EFS rate of the study regimen will be compared with historical EFS rate of 45%, which is observed in standard treatment for the study population. In order to control a two-sided type I error rate of 5%, 125 patients are needed to provide power of 99% and 92% if the true EFS rate of the augmented BFM regimen is 65% and 60%, respectively. Sample size calculation was conducted using exact test for single proportion with nQuery software.

It is impractical to carry out interim analysis based on the 3-year EFS rate. The futility monitoring rule will be based on the CR rate at 4 weeks. Using the Bayesian approach of Thall, Simon, Estey (1995, 1996) and the extension by Thall and Sung (1998), response and toxicity monitoring will be performed from the 10th patient and continue in cohort of 10. The response rate of standard regimen is 90% with toxicity rate of 33%. Therefore, the historical probability vector of (Response With Toxicity, Response Without Toxicity, No Response With Toxicity, No Response No Toxicity) is assumed to follow a Dirichlet distribution with parameters (29.7, 60.3, 3.3, 6.7), and the corresponding vector for the experimental regimen is assumed to follow a flat Dirichlet distribution with parameters (1.188, 2.412, 0.132, 0.268), which has the same response probabilities (i.e., response rate of 90%) and toxicity rate (i.e., toxicity rate of

33%). This regimen of augmented BFM will be considered worthy of further investigation if it elicits no less than 90% response rate and no greater than 33% toxicity rate. Thus, monitoring rule, assuming the prior distributions above, was constructed that meet the following condition,

$$Pr(S,Resp < E, Resp \mid data) < 0.05 \text{ for efficacy, and}$$
$$Pr(S,Tox < E, Tox \mid data) > 0.85 \text{ for toxicity.}$$

E,Resp and S,Resp are the response rates for study regimen and standard care, respectively. E,Tox and S,Tox are the toxicity rates for study regimen and standard care, respectively. These conditions will stop the study early if the data suggest that it is unlikely the response rate with this new treatment is at least as good as the standard care or the toxicity rate of new treatment is higher than the standard care.

The stopping boundary for efficacy is listed in Table 1, for example, accrual will cease if 14 or fewer responses seen in the first 20 patients.

Table1. Stop accrual if the number of patients with response is less than or equal to that indicated (i.e., # response) in the number of patients accrued (i.e., # Patients)

#Response	6	14	23	31	39	48	56
#Patients	10	20	30	40	50	60	70
#Response	65	73	81	90	98		
#Patients	80	90	100	110	120		

The stopping boundary for toxicity is listed in Table 2, for example, accrual will cease if 10 or more toxicity observed in the first 20 patients.

Table 2. Stop accrual if the number patients with toxicity is greater than or equal to that indicated (i.e., # Toxicity) in the number of patients accrued (i.e., # Patients).

#Toxicity	6	10	14	18	22	25	29
#Patients	10	20	30	40	50	60	70
#Toxicity	33	37	41	45	49		
#Patients	80	90	100	110	120		

Simulation (10,000 replicates) was used to evaluate the performance of the stopping rule on the conduct of the study (Table 3). The probability of stopping the study early when true response rate of the study regimen was 80% was at least 82%.

Table 3. Operating characteristics, based on 10,000 simulations per scenario, of

monitoring of response rates for patients treated with augmented BFM regimen.

True Rates of Response/Toxicity	Probability of Early Stopping	Achieved Sample Size Quartiles		
		25th	50th	75th
90%/20%	6%	125	125	125
90%/30%	17%	125	125	125
90%/40%	70%	20	50	125
90%/50%	99%	10	20	30
80%/20%	82%	30	40	90
80%/30%	84%	20	40	80
80%/40%	94%	10	30	50
80%/50%	99.8%	10	20	30
70%/20%	99.9%	10	20	30

Analysis Plan

Continuous variables (e.g., age, hematology values) will be summarized using the mean (s.d.) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of patient characteristics (e.g., low/high LDH) on the response rate. The distribution of time-to-event endpoints (e.g., EFS, overall survival) will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups of patients will be made using the logrank test. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes.

14.0 Protocol Compliance

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well being of the patient requires immediate intervention, based on the judgement of the investigator or his/her designee. In the event of a significant deviation from the protocol, the investigator will notify the MDACC surveillance committee following the institutional guidelines

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