THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Hyper-CVAD with Liposomal Vincristine (Hyper-CMAD) in Acute Lymphoblastic Leukemia
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Core Protocol Information

Short Title	Hyper-CVAD with Liposomal Vincristine in ALL
Study Chair:	Elias Jabbour
Additional Contact:	Jhinelle L. Graham Vicky H. Zoeller Leukemia Protocol Review Group
Department:	Leukemia
Phone:	713-792-7543
Unit:	428
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

To determine the CR rate at 1 year of hyper-CVAD plus liposomal vincristine (Marqibo) in newly diagnosed acute lymphoblastic leukemia (ALL).

To determine CR duration, toxicity and overall survival of hyper CVAD with liposomal vincristine (Marqibo) in newly-diagnosed ALL.

2.0 Background

Marqibo has been FDA approved for patients with second or greater relapsed ALL.

2.1 Acute Lymphoblastic Leukemia (ALL) and Hyper-CVAD

Following the treatment patterns in childhood ALL, results of intensive chemotherapy in adult ALL have improved outcome.[1-6] With hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high dose methotrexate and cytarabine), a dose-intensive regimen developed at MD Anderson, the results were encouraging.[7,8] From 1992 until 2000, 288 patients were treated. Their median age was 40 years; 59 patients (20%) were 60 years or older; 17% had Ph-positive ALL; 13% had T-cell ALL. The CR rate was 92%; induction mortality was 5%. The 5-year CR and survival rates were 38%. Patients with Ph-positive ALL have an improved outcome with hyper-CVAD + imatinib.[9] Patients with mature B cell ALL also have a better outcome with hyper-CVAD + rituximab.[10] Both groups are treated on separate protocols. Other improvements to the regimens have included the use of the protected environment in patients aged >/= 60 years (mortality 16%, now reduced to < 5%), adding rituximab in CD20-positive cases (CD20 positivity associated with worse prognosis), prolonging POMP maintenance therapy to 3 years with intensifications, and reducing CNS prophylaxis to 8 intrathecals for high risk disease.

2.2 Liposomal Vincristine (Marqibo)

Liposomal Vincristine was designed to reduce the neurotoxicity associated with regular vincristine. Dose-intensity of vincristine has been correlated with increased cure rates with MOPP in Hodgkin's disease. Liposomal Vincristine has produced impressive response rates of 45% in aggressive lymphoma salvage.[11] CHOP + Liposomal Vincristine in frontline lymphomas produced CR rates of 90%, overall response rates of 100%, and 2-year survival and EFS rates above 90%.[12] Phase I-II studies of Liposomal Vincristine in ALL relapse have shown encouraging response rates of 15% to 30%.[13,14] The phase II dose of Liposomal Vincristine is 2.25 mg/m^2 weekly for up to 12 doses. We propose to replace regular vincristine with Liposomal Vincristine in the hyper-CMAD regimen to evaluate long-term toxicity and efficacy of the new regimen in newly diagnosed ALL.

3.0 Background Drug Information

The background drug information for the following agents is attached as an appendix to the back of this protocol (Appendix G).

- doxorubicin
- cyclophosphamide
- methotrexate
- ara-C (cytarabine)

- MESNA
- Liposomal vincristine sulfate
- 6-mercaptopurine
- filgrastim (G-CSF)
- pegfilgrastim

3.1 Background

The dose limiting toxicity of vincristine sulfate is virtually always neurological. Neurological toxicity is dose dependent and symmetrical and is manifested as both peripheral sensory and motor neuropathy. Cranial nerve damage or encephalopathies are rare. Loss of deep tendon reflexes is the first sign of neurotoxicity. Distal parasthesias in the hands or feet and dysethesias are common if symptoms occur. With continuing administration of the drug, this can progress to severe muscle pain, weakness, gait disturbance and sensory impairment, severe weakness with foot and wrist drop. Vincristine sulfate induced peripheral neuropathies are generally reversible.

Other toxicities associated with vincristine sulfate include hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH), constipation, colicky abdominal pain, and ileus.

Cranial nerves may be affected. Extravasation of vincristine sulfate can result in painful local inflammation.

3.2 Rationale for use of Liposomal Vincristine (Marqibo) in Cancer Therapy

Due to the relatively low specificity of the interaction of cytotoxic agents with tumor tissue. Compared to healthy tissue, severe toxicities are often experienced at doses required to achieve a substantial antitumor response. Investigations over the past two decades have demonstrated that liposomal drug carriers are capable of increasing the therapeutic index of anticancer drugs by altering the drug's pharmacological behavior.

Liposomes do not accumulate in many of the tissues susceptible to vincristine-related toxicities. Consequently, liposome-encapsulated vincristine is effectively sequestered from these sites. A murine model of drug extravasation demonstrated that vincristPh-ine-induced dermal toxicity was significantly reduced by liposomal encapsulation.[16] Toxicities associated with peak blood levels and high volume of distribution of free vincristine are expected to be ameliorated by liposomal encapsulation as this provides for low blood levels over extended time periods via slow release of vincristine from the liposomes in the circulation.

In a variety of GLP and non-GLP toxicology studies comparing free vincristine with Liposomal Vincristine, there were no patterns of toxicity or unexpected toxicities due to the liposomal drug. Clinical studies have suggested that Liposomal Vincristine may be administered safely at doses exceeding those of free vincristine.

Pharmacokinetic studies in mice indicated that free vincristine given intravenously is rapidly

removed from the circulation with 0.5 - 2.5% remaining in the blood compartment 1 hour after administration. With Liposomal Vincristine, 70% of the drug remained in the circulation after the same time period.

In murine and human tumor models (L1210 and P388 leukemia, B16/BL6 melanoma and human A431 solid tumor xenografts), unencapsulated vincristine had negligible antitumor activity. Liposomal Vincristine in the same tumor models had significantly greater dose-dependent, antitumor activities. The increased antitumor efficacy of Liposomal Vincristine is consistent with liposome-mediated delivery of vincristine to the tumor site and

subsequent sustained release of the drug.

A comprehensive summary of nonclinical efficacy and safety studies is included in the Investigator's Brochure.

3.3 Clinical Studies with Liposomal Vincristine

Four clinical trials (one Phase I and three Phase II) have been conducted with Liposomal Vincristine in solid
tumors (pancreas, colorectal) and in lymphoma.

The MTD and recommended dose for further Phase II development were 2.0 - 2.4 mg/m^2 every 2 to 3 weeks. Toxicities were generally non-hematologic: myalgias, peripheral neuropathy, constipation, and fever.

Pharmacokinetic analysis suggested that Liposomal Vincristine protects the drug from rapid elimination.

In the Phase II relapsed/refractory lymphoma study (DM97-162), patients with lymphoma (intermediate grade, low grade, and transformed lymphoma) were treated with a 1-hour infusion of Liposomal Vincristine 2 mg/m^2 IV every 2 weeks.[11] Liposomal Vincristine was well tolerated. The overall response rate was 32% (26 responses in 81 evaluable patients). In patients with diffuse large cell lymphoma, 46% had a complete or partial response.

A recent study by Rodriguez et al[12] at MD Anderson Cancer Center combined CHOP substituting Liposomal Vincristine 2 mg/m^2 for VCR in newly diagnosed non-Hodgkin's lymphoma. The overall response rate was 100%; the CR rate was above 90%. The estimated 2-year survival rate was above 90%, which is extremely encouraging.

In the original Phase II protocol conducted in lymphoma-leukemia (DM97-162), 16 patients with relapsed or refractory ALL were treated with Liposomal Vincristine 2.0 mg/m^2 every 2 weeks.[13] Of 13 evaluable patients, one patient with refractory Philadelphia-positive ALL achieved CR. A second case with refractory Ph-positive ALL achieved PR. Both had been previously treated with hyper-CVAD. Significant reductions in marrow leukemia infiltrates were observed in 4 other patients.

A Phase I-II trial of liposomal vincristine weekly and pulse dexamethasone in refractory or relapsed ALL (and lymphoblastic lymphoma) also showed a response rate of 30% to 40%.[14] The Liposomal Vincristine MTD was 2.25 mg/m^2 IV weekly (up to 12 doses).

3.4 Other drug information of Liposomal Vincristine

Clinical Formulation

Spectrum Pharmaceuticals will supply Liposomal Vincristine (Marqibo)

Liposomal Vincristine consists of a three-component system designed for entrapment of vincristine sulfate at the clinical site at the time of use. The vehicle consists of sphingomyelin/cholesterol (SM/Chol) liposomes. The final drug product is prepared on site from the components in the Marqibo Kit. After preparation, each single-dose vial of Marqibo (vinCRIStine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate (Package Insert)

Table 1. Marqibo (vincristine sulfate liposomes injection) 3-vial Kit Components

COMPONENTS	TOTAL VOLUME OF EACH COMPONENT
Vincristine Sulfate Injection, USP (5 mg/5 mL)	5 mL
Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL)	1 mL
Sodium Phosphate Injection (14.2 mg/mL)	25 mL

Storage, Handling, Preparation, and Administration:

See Appendix I for details.

Drug Destruction and Handling:

All chemotherapy preparation should follow institutional guidelines for handling and destruction. Used kits will be destroyed per institutional policy. Unused kits will be destroyed according to the institutional policy at the time of expiration or study closure.

4.0 Patient Eligibility

Inclusion:

4.1 Newly diagnosed, previously untreated ALL or lymphoblastic lymphoma ≥ 18 years old. Allow urgent administration of cytarabine/hydrea/atra prior to starting treatment on protocol. Allow previous administration of up to one course of Hyper-CVAD and/or FDA approved TKI.

4.2 Zubrod performance status </= 3.

4.3 Adequate liver function (bilirubin </= 3.0 mg/dl, unless considered due to tumor), and renal function (creatinine </= 3.0 mg/dl, unless considered due to tumor).

4.4 No active co-existing malignancy with life expectancy less than 12 months due to that malignancy.

4.5 All men and women of childbearing potential who are participating in the study must agree to use effective forms of birth control throughout the duration of their treatment.

4.6 Adequate cardiac function as assessed clinically

Exclusion:

4.7 Pregnant or lactating women. Women of childbearing potential (WOCB) must have a blood or urine pregnancy test within 7 days prior to administration of the study drug. (WOCB is defined as a woman who has not undergone hysterectomy or bilateral oophorectomy and has not been naturally postmenopausal for at least 24 consecutive months).

4.8 Active Grade III-IV cardiac failure as defined by the New York Heart Association criteria,

uncontrolled angina or MI within 6 months.

4.9 Patients with medical conditions that compromise their ability to complete the study or confound interpretation of study results.

5.0 Treatment Plan

5.1 All patients will be registered through CORE.

5.2 General Considerations

- The hyper-CMAD (odd courses) will alternate with high-dose methotrexate/ara-C (even courses) administered on 21 day schedules or later to allow for recovery from myelosuppression or infection; or earlier if count recovery allows.

- Pegfilgrastim (Neulasta) 6 mg (flat dose) within 72 hours after completion of chemotherapy. G-CSF 10 μg/kg/day (rounded) until neutrophil recovery to 1 x 10^9/L or higher can be substituted or can be added if neutrophils have not recovered to 1 x 10^9 /L by day 21.

- Months of administering early and/or late Intensification maintenance courses may vary based on physician's clinical judgment and if discussed with and approved by PI.

- Next course may be started when granulocytes >/= 1.0 x 10^9/L and platelets >/= 50 x 10^9/L. These courses (Course 2 and on) may be started with or without dose reduction based on physician's clinical judgment if believed to be in the best interest of the patient when ANC <1.0 x 10^9/L and/or PLTs<50 x 10^9/L if discussed with and approved by PI.

- Rituximab 375 mg/m^2 will be given on days 1 and 8 +/- 3 days for the first 4 courses for a total of 8 doses in patients who are CD20-positive (>/= 20% expression by flow cytometry for ALL or any positivity by immunostain for lymphoblastic lymphoma). Missed doses of rituximab may be given with later courses to complete 8 doses.

- Prophylactic antibiotics will vary based on tolerance and allergy status. Suggestions include:
  -- Levofloxacin 500 mg p.o. daily (or other quinolone), trimethoprim-sulfamethoxazole double strength one tablet p.o. twice daily, or other appropriate antibacterial agent. Antibacterial antibiotics should be rotated with each cycle of intensive chemotherapy as feasible.
  -- Voriconazole 200 mg p.o. twice daily, itraconazole 200 mg p.o. twice daily, or other appropriate antifungal agent. Azole antifungal prophylaxis should be held the day before, the day of, and the day after the dose of liposomal vincristine as feasible.
  -- Valacyclovir 500 mg p.o. daily, or acyclovir 200 mg p.o. twice daily, or other appropriate antiviral agent.

- Patients identified to have Philadelphia chromosome positive (Ph+) disease will receive imatinib 600 mg daily or dasatinib 100 mg once daily on days 1 to 14 +/- 5 days of induction (course 1). On all subsequent courses the tyrosine kinase inhibitor will be given daily without interruption (imatinib 600 mg or dasatinib 70 mg). Maintenance therapy will be monthly Liposomal Vincristine and dexamethasone and continuous daily imatinib or dasatinib (no 6-MP or MTX).

- Patients identified to have Philadelphia chromosome-like disease [evaluated by

flow-cytometry and/or Fluorecent in situ hybridization (FISH) for CRLF2] will receive tyrosine kinase inhibitors (TKI) dasatinib 100 mg once daily or ruxolitinib 10-25 mg twice daily on days 1 to 14 +/- 5 days of induction (course 1). On all subsequent courses the tyrosine kinase inhibitor will be given daily without interruption. Maintenance therapy will be monthly Liposomal Vincristine and dexamethasone and continuous daily TKI.

- Maintenance chemotherapy is planned for all patients as described later. Patients may move to the maintenance therapy prior to completion of 8 cycles if they develop side effects prohibiting further intensive chemotherapy.

- Patients with mediastinal lymphoblastic lymphoma and bulky mediastinal disease (defined as >/= 7 cm) or residual mediastinal lymphadenopathy may be considered for consolidative mediastinal irradiation prior to the maintenance phase of therapy.

Other dosage adjustments are allowed if they are judged to be in the best interest of the patient, don't exceed the maximums dosages described in the protocol, and the adjustments are discussed with the study PI.

5.3 Patients aged >/= 60 years with newly diagnosed active disease, or with poor performance status, (at the discretion of the treating physician) may be induced in the protective environment. Protective environment is optional. Dosing may also be adjusted. See Section 5.7 for suggested dose modifications by age and performance status.

5.4 Central Nervous System Management

Total number of prophylactic intrathecal treatments for newly diagnosed patients (in the absence of CNS disease) will be 8 (2 intrathecals of methotrexate on day 2 $\pm$ 3 days and cytarabine day 7 $\pm$ 3 days with each course of chemotherapy until total number reached). Missed intrathecals (e.g., related to failed procedure attempts, scheduling issues, patient social situations) can be made up with subsequent courses of chemotherapy.

- High-risk disease: 8 intrathecals
  Serum lactate dehydrogenase (LDH) > 1400 U/L
  Lymphoblastic lymphoma with/without marrow involvement
  Burkitt or Burkitt-like (treated with 16 intrathecals on separate protocol)
- Patients with Philadelphia (Ph) positive ALL will receive 12 intrathecals, 2 per cycle, for the first 6 cycles. Missed intrathecals may be made up at later cycles.
- Low-risk disease: 8 intrathecals
  LDH </=1400 U/L
- Indeterminate risk: 8 intrathecals
  None of these parameters met (de novo LDH level unknown)
- If the patient has had prior intrathecal therapy or prior CNS disease, discuss management of CNS prophylaxis/therapy with the Principal Investigator.
- If active CNS disease: consider intrathecal methotrexate alternating with ara-C twice weekly until CSF clear twice; then once weekly for 4 weeks, then back to prophylactic schedule. Consider XRT to the base of the skull, if cranial nerve root involvement. Alternative methods and intratheral schedules of treating CNS disease are allowed if appropriate for the patient.

5.5 Hyper-CMAD (Courses 1, 3, 5, 7):

- Rituximab 375 mg/m^2 IV on days 1 and 8 +/- 3 days for courses 1 and 3 in patients who are CD20-positive.
- Imatinib 600 mg PO daily or dasatinib 100 mg PO daily or ruxolitinib 10-25 mg twice

daily days 1-14 +/- 5 days on course 1 and continuously (imatinib 600 mg PO or dasatinib 70 mg PO or ruxolitinib 10-25 mg twice daily) daily starting day 1 of course 2 for patients who are Ph+ or Philadelphia chromosome-like disease.

- Cyclophosphamide (CTX) 300 mg/m^2 IV over 3 +/- 1 hours approximately every 12 hours x 6 doses days 1, 2, 3 (total dose 1800 mg/m^2)
- MESNA 600 mg/m^2/d IV continuous infusion daily for 24 hours days 1-3.
- Doxorubicin 50 mg/m^2 IV over 24 +/- 2 hours via central venous catheter on day 4 after last dose of CTX given (infuse over 48 +/- 4 hours in patients with reduced ejection fractions <50%). May be given by shorter infusion if difficulty with central venous access.
- Liposomal Vincristine 2.0 mg/m^2 IV (cap at 4.0 mg total dose) over 1 hour +/- 30 minutes on days 1 and day 8 +/- 2 days.
- Dexamethasone 40 mg IV or P.O. daily days 1-4 and days 11-14 +/- 3 days.
- Pegfilgrastim (Neulasta) 6 mg (flat dose) within 72 hours after completion of chemotherapy. G-CSF 10 μg/kg/day (rounded) until neutrophil recovery to 1 x 10^9/L or higher can be substituted or can be added if neutrophils have not recovered to 1 x 10^9 /L by day 21.
- The next course may be started when granulocytes >/= 1.0 x 10^9/L and platelets >/= 50 x 10^9/L. Therapy may start earlier or later depending on the clinical situation, with a minimum of 14 days between cycles. Courses may be started with dose reductions prior to full platelet recovery, if the treatment is delayed (e.g., >/= 28 days from the last course).
- CNS prophylaxis: Methotrexate 12 mg intrathecally (6 mg if via Ommaya reservoir) day 2 +/- 3 days and ara-C 100 mg intrathecally day 7 +/- 3 days.
- Tumor lysis prophylaxis (e.g. allopurinol, intravenous alkalinization, oral bicarbonate) if indicated. Urate oxidase may substitute for allopurinol.

5.6 High-dose methotrexate and ara-C (Courses 2, 4, 6, 8):

- Rituximab 375 mg/m^2 IV on days 1 and 8 +/- 3 days for courses 2 and 4 in patients who are CD20-positive.
- Imatinib 600 mg PO daily or dasatinib 70 mg PO daily or ruxolitinib 10-25 mg twice daily without interruption for patients who are Ph+ or Philadelphia chromosome-like disease.
- Methotrexate (MTX) 200 mg/m^2 IV over 2 +/- 1 hours followed by 800 mg/m^2 IV over 22 +/- 2 hours on day 1 beginning after the completion of rituximab, if given.
- Solu-Medrol 40 mg IV approximately every 12 hours +/- 2 hours for 6 doses days 1-3 +/- 3 days.
- Ara-C 3 gm/m^2 IV over 2 +/-1 hours approximately every 12 hours for 4 doses on days 2, 3.
  - -- Reduce to 1 gm/m^2 IV over 2 +/- 1 hours approximately every 12 hours for 4 doses on days 2, 3 for:
    - o Age >/= 60 years.
    - o Creatinine >/= 1.5 mg/dl.
    - o MTX > 20 μM at time "0" (see below), confirmed on repeat sample.
    - o Neurotoxicity (grade 2 reversible cerebellar toxicity or other ara-C related CNS toxicity) with previous courses.
  - -- Consider reduction to 1 gm/m^2/day IV continuous infusion days 2, 3 for grade 2 reversible cerebellar toxicity related to ara-C 1 gm/m2, or grade 3 reversible cerebellar toxicity related to any dose of ara-C.
- Citrovorum rescue 50 mg IV followed by 15 mg IV approximately every 6 hours for 8 doses or until methotrexate level < 0.1μM beginning 12 hours +/- 2 hours post MTX

completion. Additional rescue allowed as indicated for elevated levels or delayed methotrexate clearance.

-- Check MTX levels around time 0h, 24h and 48h post completion of MTX unless cleared (e.g. 0.15 µM or less).
  - o if > 20 µM at time "0", hold ara-C and repeat level; if continues to be > 20 reduce ara-C to 1 gm/m^2 IV over 2 +/-1 hours approximately every 12 hours for 4 doses on days 2, 3.
  - o if > 1 µM at 24 hours or > 0.1 µM at 48 hours, increase citrovorum rescue until serum methotrexate level is < 0.1 µM. Clearance to levels 0.15 µM or less is acceptable in patients with normal renal function.

- Consider oral acetazolamide 250 mg p.o. b.i.d. to promote MTX excretion if the urine pH is < 7.0.
- Pegfilgrastim (Neulasta) 6 mg (flat dose) within 72 hours after completion of chemotherapy. G-CSF 10 µg/kg/day (rounded) until neutrophil recovery to 1 x 10^9/L or higher can be substituted or can be added if neutrophils have not recovered to 1 x 10^9 /L by day 21.
- The next course may be started when granulocytes >/= 1.0 x 10^9/L and platelets >/= 50 x 10^9/L. Therapy may start earlier or later depending on the clinical situation, with a minimum of 14 days between cycles. Courses may be started with dose reductions prior to full platelet recovery, if the treatment is delayed (e.g., >/= 28 days from start of last course).
- CNS prophylaxis:Ara-C 100 mg intrathecally day 5 +/-3 days and Methotrexate 12 mg intrathecally (6 mg if via Ommaya reservoir) day 8 +/- 3 days.

5.7 Suggested Dose Modifications

Suggested Dose Modifications Based on Age and Performance Status

	< 60 yrs	**60 – 74 yrs PS 0–2**	**>74 yrs > 60, PS 3–4**
Cyclophosphamide (mg/m^2)	300	250	200
Doxorubicin (mg/m^2)	50	37.5	25
Liposomal vincristine (mg/m^2)	2.0	1.6	1.2
Dexamethasone (mg)	40	20	20
Methotrexate (mg/m^2)	200 800	100 400	50 100
Cytarabine (g/m^2)	3	1	0.5

Note: Age 60 – 64 with PS 0-1 may be treated with full doses (except for reduction of cytarabine to 1 g/m2 as per design) at the discretion of the treating physician

Ara-C 1 gm/m^2 IV over 2 hours every 12 hours for 4 doses on days 2, 3:

- Creatinine >/= 1.5 mg/dl.
- Time "0" MTX level > 20 µM (on repeat level).

In older patients scheduled to receive 1 g/m^2 reduce to 0.5 gm/m^2

- Creatinine >/= 1.5 mg/dl
- Time "0" MTX level > 20 µM (on repeat level).
- Grade 2 reversible cerebellar toxicity related to high dose ara-C.

Ara-C 1 gm/m^2/day IV continuous infusion days 2, 3 for:

- Grade 2 reversible cerebellar toxicity related to ara-C 1 gm/m^2 or grade 3 reversible cerebellar toxicity related to ara-C.

Liposomal Vincristine -- reduce by 50% for bilirubin > 1.5 mg/dl and </= 3.0 mg/dL or grade 2 persistent peripheral neuropathy.

- Eliminate Liposomal Vincristine for grade 3-4 neurotoxicity, including ileus suspected to be related to vincristine, bilirubin > 3.0 mg/dL, or grade 3-4 peripheral neuropathy. When improved to Grade 0 or 1 resume at 50% of level.

Doxorubicin:

- Reduce by 50% for bilirubin >/= 2 and </= 3 mg/dl, reduce by 75% for bilirubin > 3 and </= 5 mg/dl. Eliminate if bilirubin level > 5 mg/dl.
- Administer over 48 +/- 12 hours or longer for patients with borderline/reduced (<50%) ejection fractions.

Methotrexate:

- Reduce by 25%-50% for grade 3 or worse mucositis with previous methotrexate course.
- Reduce by 50% for calculated creatinine clearance 10-50 ml/min; if < 10 ml/min, hold methotrexate.
- Reduce by 25% to 75% for delayed excretion and/or nephrotoxicity with previous methotrexate course.
- Reduce by 50% for pleural effusion or ascites (drain effusion if possible).

5.8 Imatinib/Dasatinib dose adjustments:

- Grade III-IV hepatoxicity (bilirubin > 3 x upper limit normal or elevation transaminases > 5.0 x upper limit normal)
  - Consider holding until grade I or less.
  - May resume at dose -1 level for grade III hepatotoxicity; consider discontinuing if > grade II hepatotoxicity recurs.
- Consider decrease by one dose level (e.g., imatinib 400 mg PO daily or dasatinib 50 mg PO daily) for bilirubin 1.5 - 3.0 x upper limit normal or elevation transaminases > 2.5 - 5.0 x upper limit normal.
- During intensive phase of chemotherapy, consider holding imatinib or dasatinib if ANC not > 1.0 x 10^9/L or platelet count not > 30,000 by day 21 of the cycle. Resume imatinib or dasatinib upon recovery to ANC $\geq$ 1.0 x 10^9/L and platelet count $\geq$ 50,000 (without need for G-CSF or platelet transfusions) if able to tolerate. Resume imatinib or dasatinib at prior dosing if time to recovery < 2 weeks. Resume imatinib or dasatinib with dose reductions if time to recovery > 2 weeks.
- Imatinib or dasatinib should be interrupted for clinically significant fluid retention syndrome and/or pericardial/pleural effusions. Imatinib and dasatinib may be resumed with dose reductions according to the guidelines for resolution provided for recovery from myelosuppression.
- Dose modifications for imatinib and dasatinib are guidelines only. The treatment is not required to be held if the treating physician feels it is in the patients best interest to continue treatment. Difficult cases should be discussed with the Principal Investigator.

5.9 Maintenance, intensifications, and post-remission therapy

A. Maintenance (non Ph+ positive)

- Maintenance chemotherapy with 6-mercaptopurine (6-MP), methotrexate (MTX), Liposomal Vincristine and dexamethasone (DOMP) for approximately 30 months (except for consolidations with hyper-CMAD followed by methotrexate/L-asparaginase [or vice versa] beginning at months 6 and 18) beginning at level 0 (or lower dose level if previous toxicity warrants):

-- 6-MP 50 mg tablets P.O. t.i.d. daily
-- Methotrexate 20 mg/m^2 (rounded) IV or P.O. weekly
-- Liposomal Vincristine 2.0 mg/m^2 IV (cap at 4.0 mg total dose) over 1 hour +/- 30 minutes approximately every 28 days
-- Dexamethasone 6 mg/m^2 mg P.O. daily (rounded to the nearest pill size, in divided doses twice or three times daily) days 1-5, approximately every 28 days, starting with Liposomal Vincristine (if given). Prednisone 200 mg PO daily days 1 to 5 may be substituted at the discretion of the treating physician if intolerant of dexamethasone.

- Suggested maintenance chemotherapy dose adjustments as below:

Level	MTX (mg/m2) (Rounded)	6-MP (mg/day)	Liposomal Vincristine (mg/m2)	Dexamethasone (mg/m2)	Prednisone (mg)
0	20	150	2.0	6	200
-1	15	100	1.6	4	100
-2	10	50	1.4	2	50
-3	5	50	1	0	0

Note: Doses lower and less frequent than specified in this table and combinations of these dose modifications are permitted.

- Dose adjustments for myelosuppression include methotrexate and 6-MP, but not Liposomal Vincristine or dexamethasone. Titrate to keep granulocytes > 0.75 x 10^9/L and platelet count >/= 50 x 10^9/L.

Methotrexate
- Decrease by one dose level for mucositis > grade 2
- Decrease by one dose level for bilirubin > 2.5 mg/dL or elevation transaminases >/= 5 x upper limit normal
- Hold if granulocyte count nadir < 0.5 x 10^9/L or platelets < 30 x 10^9/L, resume with decrease in one dose level or lower depending on duration of cytopenias.

6-mercaptopurine
- Decrease by one dose level for bilirubin > 2.5 mg/dL or elevation transaminases >/= 5 x upper limit normal
- Hold if granulocyte count nadir < 0.5 x 10^9/L, or platelets < 30 x 10^9/L, resume with decrease in one dose level or lower depending on duration cytopenias.

Liposomal Vincristine

Table 1. Recommended Dose Modifications for Marqibo-related Peripheral Neuropathy

Severity of Peripheral Neuropathy Signs And Symptoms[a]	Modification of Dose and Regimen
If the patient develops Grade 3 (severe symptoms; limiting self-care activities of daily living [ADL][b]) or persistent Grade 2 (moderate symptoms; limiting instrumental ADL[c]) peripheral neuropathy:	Interrupt Marqibo. If the peripheral neuropathy remains at Grade 3 or 4, discontinue Marqibo. If the peripheral neuropathy recovers to Grade 1 or 2, reduce the Marqibo dose to 1.6 mg/m^2
If the patient has persistent Grade 2 peripheral neuropathy after the first dose reduction to: 1.6 mg/m^2	Interrupt Marqibo for up to 7 days. If the peripheral neuropathy increases to Grade 3 or 4, discontinue Marqibo. If peripheral neuropathy recovers to Grade 1, reduce the Marqibo dose to 1.2 mg/m^2
If the patient has persistent Grade 2 peripheral neuropathy after the second dose reduction to 1.2 mg/m^2	Interrupt Marqibo for up to 7 days. If the peripheral neuropathy increases to Grade 3 or 4, discontinue Marqibo. If the toxicity recovers to Grade 1, reduce the. Discuss with PI

[a] Grading based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.
[b] Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
[c] Instrumental ADL: refers to preparing meals, shopping for groceries and clothes, using telephone, managing money, etc.

Reduce by 50% for bilirubin > 1.5 mg/dL, hold for bilirubin > 3.0 mg/dL.

The dose adjustments of DOMP are guidelines, and the dosing needs to be individualized to the patient, as differential toxicities between 6-MP and methotrexate may be difficult to discern. Continued antiviral prophylaxis to prevent herpes zoster is encouraged. Consider antifungal prophylaxis days of prednisone. Consider PCP prophylaxis.

B. Maintenance: Philadelphia Chromosome Positive ALL or Philadelphia Chromosome-like ALL

- Imatinib 800 mg PO daily or dasatinib 100 mg PO daily or ruxolitinib 10-25 mg twice daily indefinitely (or best tolerated dose).
- Liposomal Vincristine 2.0 mg/m^2 IV (cap at 4.0 mg total dose) over 1 hour +/- 30 minutes approximately every 28 days for 24 months
- Dexamethasone 6 mg/m^2 mg P.O. daily (rounded to nearest pill size, in divided doses twice or three times daily) days 1-5 approximately every 28 days for 24 months, starting with Liposomal Vincristine (if given). Prednisone 200 mg PO daily days 1 to 5 may be substituted at the discretion of the treating physician if intolerant of dexamethasone.
- Early and late intensifications with hyper-CMAD (and rituximab if CD20 positive) at months 6 and 18 as per intensive phase (see Section 5.5). May be omitted (with continuation of at the discretion of the treating physician if intolerant to intensive chemotherapy or if in complete molecular remission.

Continued antiviral prophylaxis to prevent herpes zoster is encouraged. Consider antifungal prophylaxis days of prednisone. Consider PCP prophylaxis.

C. Intensifications at 6 and 18 months of DOMP (Philadelphia Chromosome Negative ALL)

Early and late intensifications interrupting maintenance phase as follows:

- Two courses of chemotherapy months 6 (hyper-CMAD) and 7 (methotrexate and pegylated asparaginase) of maintenance, repeated at months 18 and 19.
  -- hyper-CMAD may precede or follow methotrexate and pegylated asparaginase

- Methotrexate 100 mg/m2 day 1 IV over 2 hours and pegylated asparaginase at a dose of 2000 IU/m2 on day 2 by IV over 2 hours and this dose will be reduced to 1000 IU/m2 on day 2 by IV over 23 hours on patients older than 60 years of age.

- Hyper-CMAD (with rituximab for CD20 positive patients)
  -- (See Section 5.5)

The length of listed medication infusion times are approximate and may run longer than described in the protocol to allow for flushing of infusion tubing and/or due to each patient's clinical situation and shall not be counted as deviations to the protocol.

5.10 Monitoring Plan

- The hyper-CVAD regimens have been conducted since 1992, and have accrued over 500 patients on similar induction-consolidation-maintenance phases. The treatment associated side-effects, both myelosuppressive and extramedullary, are well-known. Known and anticipated side effects of this regimen will not be reported as individual ADRs according to the Code of Federal Regulations and ICH guidelines-CGP Section 4.11.1, p. 24. This also complies with the NCI CTEP -CTC guidelines which state that for expected events "grade 4 myelosuppression or other grade 4 events that do not require expedited reporting will be specified in the protocol" (see Section 12.0 Reporting Requirements).

6.0 Pretreatment evaluation

Pretreatment evaluations should be completed within 30 days prior to start of drug except for pregnancy test which should be completed within 7 days of start of treatment.

6.1 History and physical examination.

6.2 CBC, platelet count, differential, creatinine, bilirubin.

6.3 Bone marrow aspirate and cytogenetics.

6.4 In patients with mediastinal disease chest x-ray or CT of the chest will be performed at baseline.

6.5 12-lead EKG

6.6 Blood or urine pregnancy test (if applicable)

6.7 Echocardiogram or MUGA to assess pretreatment ejection fraction in patients with cardiac risk factors prior to the doxorubicin infusion.

7.0 Evaluation During Study

7.1 Weekly $\pm$ 2 days CBC, platelet count and differential (when granulocytes > 1.0 x 10^9/L) for course 1, then every 2 weeks $\pm$ 2 days during courses 2-8 of chemotherapy, then every 4 weeks +/- 4 weeks during maintenance therapy and the intensive consolidation therapy.

7.2 Bilirubin, creatinine weekly ± 2 days for course 1, then every 2 weeks ± 2 days during courses 2-8, then every 4 weeks +/- 4 weeks during maintenance therapy and the intensive
consolidation therapy.

7.3 Bone marrow aspiration for course 1 day 14 +/- 5 days and 1-2 weeks +/- 5 days later to confirm response. Bone marrow aspiration will then be done every 3-6 months to monitor disease as feasible. Omitted or missed bone marrow aspirations will not be considered protocol deviations.

7.4 Follow up Chest x-ray or CT scan in patients with mediastinal disease to document CR after cycle 1 of therapy and then as indicated every 3 to 6 months.

8.0 Criteria for Response

8.1 Complete Remission: Normalization of the peripheral blood and bone marrow with 5% or less blasts in a normocellular or hypercellular marrow with a granulocyte count of 1 x 10^9/L or above and platelet count of 100 x 10^9/L or above. Complete resolution of extramedullary disease.

8.1.1 Complete remission with incomplete platelet recovery (CRp). As per CR but platelet count < 100 x 10^9/L.

8.1.2 Complete remission with incomplete recovery (CRi). As per CR but platelet count < 100 x 10^9/L or absolute neutrophil count < 1 x 10^9/L.

8.2 Partial Remission (PR): As above for CR except for the presence of 6-25% marrow blasts or for lymphoblastic lymphoma without marrow disease, >/= 50% decrease in tumor size.

9.0 Evaluation of Toxicity

9.1 The CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have acccess to a copy of the CTEP Version 4 of CTCAE.

10.0 Criteria for Removal from the Study

10.1 Progressive disease

10.2 Non-compliance by the patient with protocol requirements.

10.3 Patient's request to be removed from the study.

11.0 Statistical Considerations

This is a single-arm, open-label, phase II clinical trial to evaluate the efficacy and safety of liposomal vincristine (Marqibo), replacing standard vincristine in the Hyper-CVAD (HCVAD) regimen, for the treatment of newly diagnosed, previously untreated acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma.

Since liposomes do not accumulate in many tissues susceptible to vincristine-related toxicities, the toxicity profile of Liposomal Vincristine, especially neurotoxicity is improved relative to standard vincristine. Thus the potential for increasing dose intensity and hopefully cure exists. Since neurotoxicity is the dose limiting toxicity with vincristine, grade 3 or 4 neurotoxicity at 6 months will be monitored in this study. Since the dose intensity of Liposomal Vincristine is higher than for standard vincristine, we will simultaneously monitor the complete remission rate at one year. Accrual is estimated at 1 to 2 patients per 6 months. A maximum of 65 patients will be enrolled in this study on an intent-to-treat basis; total study duration is thus estimated as 4 to 5 years.

Sample Size and Endpoint Monitoring

The Bayesian approach of Thall et al. (1995, 1996) with the extension by Thall and Sung (1998) will be used to simultaneously monitor CR rate at one year and 6-month grade 3 or 4 neurotoxicity. 264 ALL patients treated with HCVAD experienced a 95% induction CR rate. At 1, 2, and 3 years the CR rates were 70%, 55%, and 46%. The 6-month neurotoxicity rate in this population is approximately 15%. For the prior distribution of HCVAD with standard vincristine, we assumed a simple Dirichlet distribution and independence between 1-year CR rate and neurotoxicity in 132 patients. The parameters for this prior distribution are presented in table 1.

Table 1. Dirichlet parameters for the joint prior distribution of objective response and infection rate assuming information on 132 patients and independence among response and infection

	CR rate at 1 Year	Others
Grade 3 or 4 Neurotoxicity in first 6-months of HCVAD	14	6
Others	78	34

A flat Dirichlet prior distribution for HCVAD with Liposomal Vincristine was chosen reflective of information from the equivalent of 2 patients with the same marginal distributions as for HCVAD alone (e.g., 1-year CR rate of 70% and neurotoxicity rate of 15%).

This regimen of HCVAD with Liposomal Vincristine will be considered worthy of further investigation if it elicits an increase in 1-year CR rate to 80% with acceptable toxicity. A 25% 6-month grade 3 or 4 neurotoxicity rate is considered unacceptable. Thus, interim monitoring rules, assuming the prior distributions above, were constructed as below. The trial will be stopped if,

1) $Pr(\theta_{S,NeurTox} + 0.1 < \theta_{E,\ NeurTox} \mid data) > 0.80$, or
2) $Pr(\theta_{S,CR1} + 0.1 < \theta_{E,\ CR1} \mid data) < 0.05$

Where θ_S and θ_E are the true toxicity and 1-year CR rates for HCVAD with standard vincristine and VSLI, respectively. The first rule provides for stopping the study if excessive toxicity is highly probable (i.e., probability >80%) for the new regimen. The second condition will stop the study early if the data suggest that it is unlikely (i.e., probability < 5%) that 1-year CR rate of HCVAD with VSLI is 10% better than the historical 1-year CR rate for patients treated with standard vincristine. The maximum number of patients enrolled will be 65 patients.

The monitoring rule for 6-month grade 3 or 4 neurotoxicity, based on these assumptions and monitoring conditions is found in table 2. For example, accrual will cease if 3 patients experience grade 3 or 4 neurotoxicity in the first 6 months of treatment among the first 3 to 6 patients treated.

Table 2. Stop accrual if the number patients experiencing grade 3 or 4 neurotoxicities in the first 6 months of HCVAD with VSLI is equal to or greater than indicated (#Toxicities) among the number of patients accrued (# Patients).

# Toxicities	3	4	5	6	7	8	9	10	11	12	13
# Patients	3-6	7-9	10-12	13-15	16-19	20-22	23-26	27-29	30-32	33-36	37-39
# Toxicities	14	15	16	17	18	19	20				
# Patients	40-43	44-46	47-50	51-53	54-57	58-60	61-64				

Monitoring 1 Year CR rate will be based on the Table 3. For example, accrual will cease if 5 or fewer patients are in CR at one year in the first 10 patients treated or if there are 26 or fewer CRs at one year for the first 40 patients.

Table 3. Stop accrual if the number patients in CR at one year is less than or equal to that indicated (# CR-1's) in the number of patients accrued (# Patients).

# CR-1's			2	3	4	5	6	7	8	9	2
# Patients			5	7	9	10	11	13	14	16	5
# CR-1's	10	11	12	13	14	15	16	17	18	19	20
# Patients	18	19	20	21-22	23	24-25	26	27-28	29	30	31-32
# CR-1's	21	22	23	24	25	26	27	28	29	30	31
# Patients	33	34-35	36	37	38-39	40	41-42	43	44	45-46	47
# CR-1's	32	33	34	35	36	37	38	39	40	41	42
# Patients	48	49-50	51	52-53	54	55	56-57	58	59-60	61	62
# CR-1's	43										
# Patients	63-64										

Simulation (10,000 replicates) was used to evaluate the performance of these stopping rules on the conduct of the study. The operating characteristics of the stopping rules are listed in the following table.

Table 4. Operating characteristics, based on 10,000 simulations per scenario, of simultaneous monitoring 1-Year CR rate and 6-month grade 3 or 4 neurotoxicity in patients treated with HCVAD using liposomal vincristine.

1-Year CR rate/6-month Neurotoxicity Relationship	True CR/Neurotoxicity Rates	Probability Of Stopping	Achieved Sample Size Quartiles		
			25^{th}	50^{th}	75^{th}
Low / Low	70%/15%	0.68	8	27	65
Low / High	70%/25%	0.80	6	14	48
Intermediate / Low	80%/15%	0.22	65	65	65
Intermediate / High	80%/25%	0.52	8	50	65
High / Low	90%/15%	0.09	65	65	65
High / High	90%/25%	0.44	12	65	65

Analysis Plan

The primary end point is the CR rate at one year for the hyper-CVAD plus liposomal vincristine in newly

diagnosed ALL.

Secondary endpoints include CR duration, overall survival and toxicities.

Since the CR rate at one year by the standard HCVAD is 70%, the new regime of HCVAD with Liposomal Vincristine will be considered worthy of further investigation if it elicits an increase in 1-year CR rate to 80% with acceptable toxicity. A lower than 25% 6-month grade 3 or 4 neurotoxicity rate is considered acceptable. The CR rate at one year will be calculated as the total number of patients who are in CR at one year divided by the total number of patients who received at least one dose of HCVAD with Liposomal Vincristine. Patients who dropped out before one year will be counted as failures. Logistic regression analysis will be conducted for the primary end point, i.e., CR at one year. More analysis details are described below.

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 6-month neurotoxicity rates and CR rates. The distribution of time-to-event endpoints (e.g., CR duration, 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.

References

Thall, PF, Simon, R, Estey, EH: Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statistics in Medicine* 14:357-379, 1995.

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12.0 Reporting Requirements

12.1 Adverse events will be documented in the medical record and entered into PDMS/CORE according to Appendix D. The investigator is responsible for determining the attribution of adverse events to study drug(s).

12.2 Adverse Events Requiring Expedited Reporting: Serious unexpected adverse events (SAEs) considered associated therapy should be reported to the Principal Investigator. All AEs should be reported to the study nurse.

12.3 Events include those known toxicities or side effects related to the components of the chemotherapy. Grade 4 or less events that are known toxicities or known side effects related to the components of the chemotheray or supportive therapy will not be reported as individual SAEs, but will be summarized in the annual report to the IRB~~:~~.

12.4 Events not considered to be serious events are hospitalization for the routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

12.5 Leukemia/myelosuppression related events. [from other protocols]

12.6 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience - any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity - a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **The MDACC “Internal SAE Report Form for Prompt Reporting” will be used for reporting to the IND Office.**

- **Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Office according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Concomitant medications will not be added to the case report form but will be documented in the electronic medical record (Clinicstation).

13.0 References

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Consent Revision Date: 11/11/2016

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Hyper-CVAD with Liposomal Vincristine (Hyper-CMAD) in Acute Lymphoblastic Leukemia
2008-0598

Subtitle: Hyper CVAD

Study Chair: Elias Jabbour

1.

Participant's Name _____ Medical Record Number _____

You are being asked to take part in this clinical research study at The University of Texas MD Anderson Cancer Center ("MD Anderson"). This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to take part in the study.

You are being asked to take part in this study because you have acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma.

If you are reading and signing this form on behalf of a potential participant, please note: Any time the words "you," "your," "I," or "me" appear, it is meant to apply to the potential participant.

2. PURPOSE OF STUDY

The goal of this clinical research study is to learn if intensive chemotherapy (hyper-CVAD therapy) given in combination with liposomal vincristine (Marqibo), in addition to rituximab for patients who are CD20 positive and/or imatinib or dasatinib for patients with the Philadelphia (Ph) chromosome, can help to control ALL or lymphoblastic lymphoma. The safety of this treatment will also be studied. CD20 is a protein "marker" that is found in leukemia or lymphoma cells.

3. DESCRIPTION OF STUDY

The Study Drugs

Adriamycin (doxorubicin) is designed to stop the growth of cancer cells, which may cause the cells to die.

Cyclophosphamide is designed to disrupt with the multiplication of cancer cells, which may slow or stop their growth and spread throughout the body. This may cause the cancer cells to die.

Cytarabine (Ara-C) is designed to insert itself into DNA (the genetic material of cells) of cancer cells and stop the DNA from repairing itself.

Dexamethasone is a corticosteroid that is similar to a natural hormone made by your body.

Methotrexate is designed to disrupt cells from making and repairing DNA and "copying" themselves.

Vincristine is designed to disrupt the multiplication of cancer cells, which may slow or stop their growth and spread throughout the body. This may cause the cancer cells to die.

Liposomal Vincristine (Marqibo) is designed to help vincristine stay in the bloodstream for a longer time, more specifically target tumor tissue, and deliver more of the drug to a tumor site over a longer period of time. This may increase how effective the drug is and lower the risk of possible side effects in healthy, non-tumor tissue.

Rituximab is a monoclonal antibody that is designed to attach to leukemia cells and activate a series of events that may cause the cancer cells to die.

Tyrosine Kinase Inhibitors (TKI--Imatinib or Dasatinib)
Imatinib is a drug designed to block cancer cells from growing and dividing. **Dasatinib** is designed to block a protein that cancer may need to grow, survive, or spread.

Screening Tests
Signing this consent form does not mean that you will be able to take part in this study. You will have "screening tests" to help the doctor decide if you are eligible to take part in this study. The following tests and procedures will be performed:

- Your complete medical history will be recorded.
- You will have a complete physical exam, including measurement of your height, weight, and vital signs (blood pressure, breathing rate, heart rate, and temperature).
- You will have an electrocardiogram (ECG - a test to measure the electrical activity of the heart).
- An echocardiogram (ECHO) or multigated acquisition (MUGA) scan will be performed to check the pumping function of your heart.
- Blood (about 7 tablespoons) will be drawn for routine tests.
- Blood (about 1 teaspoon) or urine will also be collected for a pregnancy test for women who are able to become pregnant. To take part in this study, the pregnancy test must be negative.
- If the study doctor thinks it is needed, computerized tomography (CT) scans of the chest will be performed to check the status of the disease. The study doctor will decide how many scans you will have.
- A bone marrow aspirate will be performed to check the status of the disease. To collect a bone marrow aspirate, an area of the hip bone is numbed with anesthetic and a small amount of bone marrow is withdrawn through a large needle.
- If you have lymphoblastic lymphoma, a chest X-ray will be performed to check the status of the disease.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Study Groups
If you are found to be eligible to take part in this study, you will be assigned to 1 of 2 groups, based on your already performed diagnostic test for a certain protein, called CD20.

- If you test positive for CD20, you will receive hyper-CVAD therapy plus rituximab.
- If you test negative for CD20, you will receive hyper-CVAD therapy only.

In addition, patients with the Philadelphia chromosome (considered Philadelphia-positive or Ph+) will receive imatinib or dasatinib in either group. The study doctor will decide which drug these participants will receive.

Study Drug Administration
Hyper-CVAD therapy is a combination of 7 chemotherapy drugs: the combination of adriamycin (doxorubicin), cyclophosphamide, and liposomal vincristine, alternating with the combination of cytarabine (Ara-C), dexamethasone, methotrexate, and liposomal vincristine. You will receive the 2 different study drug combinations over 21-28 day "courses." You will begin with Course A treatment and alternate with the Course B treatment every other course. You will stay overnight in the hospital for the first 4-5 days of each course.

For Course A of treatment, you will receive cyclophosphamide, liposomal vincristine, doxorubicin, and dexamethasone.

For Course B of treatment, you will receive methotrexate, cytarabine, and liposomal vincristine.

Courses of treatment on this study will continue to alternate or switch between the Course A study drug combination for all odd number courses (3, 5, and 7) and the Course B study drug combination for all even number courses (4, 6, and 8) for a total of up to 8 courses.

While you are on study, all doses of study drug combinations will be given through a central venous catheter (CVC). A CVC is a sterile flexible tube that will be placed into a large vein while you are under local anesthesia. Your doctor will explain this procedure to you in more detail, and you will be required to sign a separate consent form for this procedure.

Course 1:
On Days 1, 2, and 3 you will receive cyclophosphamide by vein over about 24 hours, mesna by vein continuously over 24 hours, and liposomal vincristine by vein over 1 hour +/- 30 minutes (Day 1 only). Mesna is given to help prevent blood in the urine, which is sometimes caused by cyclophosphamide.

On Days 2 and 7, methotrexate then cytarabine will be given by intrathecal (IT) infusion directly into your spinal fluid to lower the risk of the disease spreading to the brain.

On Day 4, you will receive doxorubicin by vein over 24 hours.

On Day 5 or 6, G-CSF will be injected under the skin to help with the recovery of bone marrow cells recovery 24 hours after the dose of study drugs.

On Day 8, you will receive liposomal vincristine by vein over 1 hour +/- 30 minutes.

On Days 1-4 and Days 11-14, dexamethasone will be given by mouth with a glass of water or by vein as a short infusion.

CD20 positive patients only will also receive rituximab by vein over 6 hours, on Days 1 and 8, in addition to receiving all study drugs, as described above. If you are CD20 negative, you will not receive rituximab.

Ph+ participants will receive imatinib by mouth with breakfast and a large glass of water (about 8 ounces) or dasatinib by mouth on Days 1-14 during Course 1.

Course 2:
On Day 1, you will receive methotrexate by vein over 24 hours.

On Days 2 and 3, you will receive cytarabine by vein over 2 hours every 12 hours for a total of 4 doses. You will also be given citrovorum factor (leucovorin) by vein or by mouth to help prevent the possible side effects of methotrexate.

On Day 5 or 6, G-CSF will be injected under the skin to help with bone marrow recovery 24 hours after the dose of study drugs.

On Days 5 and 8, cytarabine then methotrexate will be given by IT infusion to lower the risk of the disease spreading to the brain.

CD20 positive patients only will also receive rituximab by vein over 4 hours, on Days 1 and 8, in addition to receiving all study drugs, as described above. If you are CD20 negative, you will not receive rituximab.

Ph+ participants will receive imatinib by mouth with breakfast and a large glass of water (about 8 ounces) every day during Courses 2-8. Dasatinib will be given by mouth every day during Courses 2-8.

Course 1 Study Visits

- Blood (about 5 teaspoons each time) will be drawn weekly for routine tests**.**
- **During Week 2 and 3 or 4**, a bone marrow aspirate will be performed to check the status of the disease.
- **At the end of Course 1**, if the study doctor thinks it is needed, a chest X-ray or CT scan will be performed to check the status of the disease.

If the study doctor thinks it is needed, any of these tests may be repeated at any time while you are receiving the study drug combination.

Radiation Treatment
If you have lymphoblastic lymphoma and you have enlarged lymph glands in the chest, you may receive radiation treatment to the chest after completing 8 courses of therapy and before you begin maintenance therapy. If you are to receive radiation therapy to the chest, the study doctor will discuss this procedure and its known risks with you in more detail, and you will be given a separate consent form to sign.

Maintenance Therapy -- Non-Ph+ Participants

After completing 8 courses of the study drug combinations, you will begin maintenance therapy for a total of 30 months, and will be interrupted by 2 periods of intensive chemotherapy consolidation courses.

Every month during maintenance therapy:

- You will take 6-mercaptopurine every day by mouth.
- You will receive methotrexate by vein or mouth 1 time every week.
- You will receive liposomal vincristine by vein over 1 hour +/- 30 minutes on Day 1.
- You will take dexamethasone by mouth on Days 1-5 each month.

First intensive chemotherapy consolidation courses:

- Six (6) months after you begin maintenance therapy, you will receive two months of intensive chemotherapy courses.
- First, you will receive cyclophosphamide, liposomal vincristine, doxorubicin, and dexamethasone (similar to Course 1) for Month 6 of therapy.
- About one (1) month later, you will receive methotrexate by vein (at a lower dose than given during Course 2) on Day 1 and pegylated asparaginase by vein over about 2 hours on Day 2. You will be given each drug 1 time each week for a total of 4 weeks for Month 7 of therapy.

About eighteen (18) months after you begin maintenance therapy, you will repeat the intensive chemotherapy courses just described.

Maintenance Therapy -- Ph+ Participants
After completing 8 courses of the study drug combinations, you will begin maintenance chemotherapy plus imatinib or dasatinib. Maintenance chemotherapy will be given for a total of 24 months, and will be interrupted by 2 periods of intensive chemotherapy courses and imatinib or dasatinib at 6 and 13 months from the start of maintenance. You will continue receiving imatinib or dasatinib every day from that point on, unless intolerable side effects occur.

Every month during maintenance therapy:

- You will take imatinib or dasatinib every day by mouth.
- You will receive liposomal vincristine by vein over 1 hour +/- 30 minutes on Day 1.
- You will take dexamethasone by mouth on Days 1-5 each month.

Intensive chemotherapy consolidation courses:

- At six (6) and eighteen (18) months after you begin maintenance therapy**,** you will receive two months of intensive chemotherapy courses. You will receive cyclophosphamide, liposomal vincristine, doxorubicin, and dexamethasone with imatinib or dasatinib (similar to Course 1). If the disease is CD20 positive, you may receive rituximab.

Blood Tests
During maintenance therapy and the intensive consolidation therapy, you will have blood (about 5 teaspoons) drawn every 4 weeks +/- 4 weeks for routine tests.

After intensive chemotherapy consolidation, for as long as you continue to receive maintenance therapy, blood (about 5 teaspoons) will be drawn every 4 weeks +/- 4 weeks, until maintenance therapy is completed:

Additional Tests while on Study
Every 3-6 months:

- You will have a bone marrow biopsy performed to check the status of the disease.
- If you have mediastinal disease, you will have a chest x-ray or CT scan.

Length of Study
You will receive up to 8 courses of therapy. If you are not Ph+, you will continue to receive maintenance therapy for up to 30 months. If you are Ph+, you will continue to receive maintenance therapy for up to 24 months, followed by imatinib or dasatinib alone indefinitely. You will be taken off the study if disease gets worse, you experience intolerable side effects, or the study doctor thinks it is in your best interest.

Additional Information
If you are 60 years or older, you will receive Course 1 chemotherapy in a protective isolation room to decrease the risk of any infection(s) that you may be exposed to while receiving the Course 1 treatment.

This is an investigational study. Liposomal vincristine is FDA approved for the treatment of patients with CLL who have relapsed at least 2 times. All of the other study drugs used in this study are FDA approved and commercially available. The combination of liposomal vincristine with the other study drugs is also being used in research only.

Liposomal vincristeine will be provided at no cost to you while you are enrolled in this study. You and/or your insurance provider will be responsible for all other drugs that are given to you as part of this study.

Up to 65 patients will take part in this study. All will be enrolled at MD Anderson.

4. RISKS, SIDE EFFECTS, AND DISCOMFORTS TO PARTICIPANTS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Tell the study staff about any side effects you may have, even if you do not think they are related to the study drug.

Imatinib, dasatinib, doxorubicin, cyclophosphamide, cytarabine, liposomal vincristine, and rituximab each may cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.

Imatinib Side Effects

Common (occurring in more than 20% of patients)

• swelling • fatigue • fever • headache • skin rash and/or itching • abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)	• nausea • diarrhea • vomiting • gas • abdominal pain • loss of appetite • weight gain • upset stomach • low blood cell counts (white, red, and/or platelets)	• pain • weakness • cramps • abnormal liver tests (possible liver damage) • teary eyes • abnormal kidney test (possible kidney damage) • cough • difficulty breathing

Occasional (occurring in 3-20% of patients)

• chest pain • irregular heartbeat • low blood pressure (possible dizziness/fainting) • high blood pressure • low oxygen levels in the blood (possible light-headedness) • bleeding in the brain • depression • dizziness • difficulty sleeping • anxiety • chills/shivering • hair loss (partial or total) • sweating (possible night sweats)	• skin sensitivity to sunlight or lamps • dry skin • high blood sugar (possible diabetes) • abnormal digestive blood test (possible inflammation of the pancreas) • constipation • mouth blisters/sores (possible difficulty swallowing) • weight loss • abdominal swelling • abnormal taste • digestive system bleeding	• inflammation of the stomach and/or intestines • abnormal liver tests (possible yellowing of the skin and/or eyes) • abnormal liver and bone tests • abnormal sensations (such as pins and needles) • blurry vision • painful red eyes • sore throat • runny nose • build-up of fluid around the lungs • flu-like symptoms

Exact frequency unknown but occurring between 1% to 10%

• numbness • flushing • skin redness • changes in nail color/appearance • heartburn	• dry mouth • increase in infection-fighting cells • nerve damage (possible numbness, pain, and/or loss of motor function)	• bleeding in the tissue lining the eye • dry eyes • nosebleed

Rare but serious (occurring in fewer than 3% of patients)

• chest pain due to heart trouble • tissue swelling • shock caused by heart damage • severe heart problems (such as heart attack and/or heart failure) • sudden stopping of the heart • build-up of fluid in the tissue around the heart (possible heart failure) • fast heartbeat • blood clot in either the vein or artery (possible pain, swelling, and/or redness) • increased pressure between the skull and brain (possible vision changes and/or headaches) • swelling of the brain (possible headache and/or mental status changes) • seizure • memory loss • fainting • allergic skin reaction • very severe blistering skin disease (loss of large portion of skin) • shedding and scaling of the skin (possible fatal loss of bodily fluids) • skin condition with fever and skin lesion • red, dry, scaly patches of thickened skin (psoriasis) • hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering) • very severe blistering skin disease (with ulcers of the skin and digestive tract)	• blistering skin rash • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • stomach ulcer • intestinal blockage • hole in the intestines (possibly leaking contents into the abdomen) • vomiting of blood • dehydration • tarry or coffee ground-like blood in the stool • fluid in the abdomen • inflammation of the pancreas (possible abdominal pain) • heavy/irregular menstrual bleeding • swelling of the scrotum • bleeding ovarian cyst (fluid-filled lump) • blood in the urine • anemia due to destruction of red blood cells • blood vessel inflammation (possible bleeding and/or bruising) • blood vessel disorder causing painful, cold, numb, and discolored fingers and/or toes • high blood platelet count (possible increased clotting) • bleeding in or from the tumor • breakdown products of the cancer cells entering the bloodstream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)	• blood vessel blockage • liver damage and/or failure (possibly due to inflammation) • breakdown of muscle tissue (possible kidney failure) • hip bone destruction • pain in the hip/leg due to loss of blood supply • bleeding in the eye • swelling under the central part of the retina and/or of the eye nerve (possible vision loss) • increased pressure in the eye (possible vision loss) • cataracts (clouding of the lens of the eye) • hearing loss • kidney failure • high blood levels of uric acid (possible painful joints and/or kidney failure) • lung damage and/or inflammation (possible difficulty breathing) • bleeding in the lungs and/or airways • increased blood pressure in the lungs (possible difficulty breathing and/or heart failure) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Studies in rats have shown an increased risk of developing tumors of the kidney, bladder, and/or female organs, both non-cancerous and cancerous, when receiving doses of imatinib mesylate that are 0.5 to 4 times higher than the dose level commonly given to humans. To date, there is no information available on the risk of these events occurring in humans.

If you can become pregnant, imatinib may cause miscarriage and/or birth defects.

Dasatinib Side Effects

Common (occurring in more than 20% of patients)

• swelling • headache • fatigue • skin rash (possible itching, blistering, shedding, irritation, and/or redness)	• hives • allergic skin reaction • white skin bumps • diarrhea • nausea • low blood cell counts (red, white, platelets)	• build-up of fluid in and/or around the lungs (possible difficulty breathing) • difficulty breathing

Occasional (occurring in 3-20% of patients)

• build-up of fluid in the tissue around the heart • decreased blood supply to the heart • heart failure • severe heart problems • enlarged heart • fever • central nervous system bleeding	• constipation • vomiting • abdominal pain • digestive system bleeding • abnormal liver tests (possible liver damage or yellowing of the skin and/or eyes)	• pain (joint/bone/muscle) • muscle spasms • abnormal kidney test (possible kidney damage) • increased blood pressure in the lungs (possible difficulty breathing and/or heart failure) • infection

Exact frequency unknown but occurring in between 1 and 10% of patients:

• irregular/fast heartbeat • chest pain • flushing • high blood pressure • chills • depression • dizziness • difficulty sleeping • acne • hair loss (partial or total) • eczema (skin inflammation) • dry skin • sweating • high blood levels of uric acid (possible painful joints and/or kidney failure)	• abdominal swelling • loss of appetite • upset stomach • inflammation of the stomach and/or intestines • mouth blisters/sores (possible difficulty swallowing) • abnormal taste • weight loss/gain • nerve damage (possible numbness, pain, and/or loss of motor or sensory function)	• weakness • blurry vision (possible loss of vision) • dry eyes • vision problems • ringing in the ears • cough • lung inflammation (possible difficulty breathing) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Rare but serious (occurring in fewer than 3% of patients)

• chest pain due to heart trouble • low blood pressure (possible dizziness/fainting) • heart attack • sudden stopping of the heart • enlarged heart • heart and lung failure • heart inflammation • inflammation of the tissue around the heart (possible chest pain) • abnormal blood test (possible heart	• inflammation of the thyroid gland (possible tenderness in the neck) • overactive thyroid gland (possible weight loss, heart rate changes, and/or sweating) • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • high blood levels of fat (possible heart disease and/or stroke) • low blood levels of albumin (possible swelling, weakness,	• blood clots in a vein (possible pain, swelling, and/or redness) • abnormal blood clotting • blockage of the bile tract (possible body yellowing and/or abdominal pain) • liver damage • paralysis of nerves controlling the head and neck • bone destruction • eye bleeding • inflammation of an eye nerve

problems) • stroke • temporary stroke symptoms • seizure • memory loss • dementia (loss of mental capacity) • fainting • difficulty walking • inflammation of the fatty layer under the skin • skin condition with fever and skin lesions • painful skin bumps • hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering) • very severe blistering skin disease (with ulcers of the skin and digestive tract)	and/or fatigue) • diabetes • fluid in the abdomen • dehydration • gum bleeding • stomach ulcer • abnormal connections or passageways between organs or vessels • intestinal blockage • gallbladder inflammation (possible abdominal pain) • severe inflammation of the pancreas (possible sudden abdominal pain) • blood in the urine • uterine and/or vaginal bleeding • decreased bone marrow function and inability to make red blood cells • blood vessel blockage	• hearing loss • kidney failure • breakdown of muscle tissue (possible kidney failure) • difficulty breathing due to narrowing of the airways • blockage in the lung (possible pain, shortness of breath, and/or failure to breathe) • coughing up blood • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage) • allergic reaction

Dasatinib may cause harm to a fetus if taken during pregnancy.

Other Instructions about Dasatinib

Call your doctor at the first sign of diarrhea. You should keep some Loperamide (Imodium) at home, in case you have diarrhea. You should call your doctor right away or go to the hospital if there are any signs of bleeding from your stomach (vomiting bloody or dark stomach contents) or bleeding from the intestines (dark or bloody bowel movements).

Call your doctor right away, and go to a hospital if you have signs of heart problems such as abnormal heartbeat or chest discomfort.

Anybody other than the participant should wear protective gloves when handling dasatinib.

You should not eat grapefruit or drink grapefruit juice while taking dasatinib.

<u>Doxorubicin Side Effects</u>

It is not known how often the side effects of doxorubicin may occur.

• irregular, slow, and/or fast heartbeat • abnormal ECG • extra heartbeats • severe heart problems • heart failure • heart inflammation • inflammation of the tissue around the heart (possible chest pain) • fatigue/lack of energy • chills • coma • fever • seizure • shock • nerve damage (possible numbness, pain, and/or loss of motor function) • skin rash • itching • hives • skin sensitivity to sunlight or lamps • severe sunburn-like rash at site of previous radiation (called radiation recall)	• very severe blistering skin disease (with ulcers of the skin and digestive tract) • very severe blistering skin disease (loss of large portion of skin) • hair loss (partial or total) • discoloration of saliva, sweat, urine, or tears • darkening of the skin, nail, and/or mouth • stopped menstrual cycle • dehydration • inability to have children • problems with production of sperm and eggs • high blood levels of uric acid (possible painful joints and/or kidney failure) • abdominal pain • loss of appetite • death of colon tissue • diarrhea • stomach and/or small intestine ulcer • mouth blisters/sores	• nausea • vomiting • low blood cell counts (red and platelets) • decreased bone marrow function (possible leukemia) • vein hardening • growth failure • abnormal liver tests (possible yellowing of the skin and/or eyes) • liver damage due to inflammation • weakness • painful red and/or teary eyes • eye inflammation • lung damage at the site of prior radiation • infection • injection site pain and/or inflammation • allergic reaction, which may be life-threatening (including hives, itching, tissue swelling, difficulty swallowing, and difficulty breathing)

Doxorubicin may cause you to develop another type of cancer (such as secondary acute myelogenous leukemia, a type of blood cancer).

Cyclophosphamide Side Effects

It is not known how often the following side effects may occur:

• hair loss (partial or total) • mouth blisters/sores (possible difficulty swallowing) • nausea • vomiting • abdominal pain	• loss of appetite • diarrhea • problems with production of sperm and eggs • inability to have children • stopped menstrual cycle	• low blood counts (red, platelet, white) • bladder inflammation and bleeding (possible pain and/or urge to urinate) • infection

Cyclophosphamide may cause you to develop another type of cancer (such as bladder cancer, acute leukemia [a type of blood cancer], lymphoma [a type of lymph node cancer], thyroid cancer, cancer of the bone marrow, and/or sarcoma [a type of cancer that can start in the soft tissue, bone, or other tissue].

Rare but serious (occurring in fewer than 3% of patients)

• irregular heartbeat • build-up of fluid around the heart (possible heart failure) • inflammation of the heart and/or the tissue around the heart (possible chest pain and/or bleeding) • heart damage/failure, death of heart tissue, or other severe heart problems • blood clots in a vein (possible pain, swelling, and/or redness) • blood clots in an artery (possible organ damage such as stroke and/or heart attack) • brain injury that may be reversible (possible headache, confusion, seizures, and/or vision loss) • dizziness • very severe blistering skin disease (with ulcers of the skin and digestive tract) • severe sunburn-like rash at site of previous radiation (called radiation recall) • wound healing problems • very severe blistering skin disease (loss of large portion of skin)	• low blood levels of potassium (possible weakness) • low blood levels of sodium (possible headache, confusion, seizures, and/or coma) • hormonal deficiency that affects the body's ability to control blood pressure and react to stress • decreased supply of blood to the abdomen • digestive system bleeding • enlarged bowel (possible abdominal pain) • inflammation of the intestines (possible bleeding) • inflammation of the pancreas (possible abdominal pain) • liver damage (possibly due to blood clots) • jaundice (yellowing of skin and/or eyes) • high blood levels of uric acid (possible painful joints and/or kidney failure) • ovarian scarring • urinary tract or bladder scarring • decreased testicle size and function • blood in the urine • blurry vision	• hearing loss • breakdown of muscle tissue (possible kidney failure) • death of kidney tissue (possible kidney failure) • difficulty breathing • lung inflammation (possible difficulty breathing) • problems with blood carrying oxygen (possible blue skin) • lung damage due to blood clots • increased blood pressure in the lungs (possible difficulty breathing and/or heart failure) • multiorgan failure • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Cytarabine Side Effects

Frequent:

• fever • skin rash • anal and/or rectal inflammation • anal sores • loss of appetite	• diarrhea • mouth sores and/or blisters • nausea • vomiting • low blood cell counts (red, white, platelet)	• abnormal liver tests (possible liver damage) • abnormal liver tests (possible yellowing of the skin and/or eyes • blood clots in a vein (possible pain, swelling, and/or redness)

Less Frequent:

• chest pain • inflammation of the tissue around the heart (possible chest pain) • dizziness • headache • nerve damage (possible dizziness and/or headache) • inflammation of nerves (possible pain and/or loss of motor or sensory function) • hair loss (partial or total) • itching	• skin freckling • skin sores • hives • abdominal pain • death of tissue in the intestines • esophageal sore • throat inflammation • inflammation of the pancreas (possible abdominal pain) • sore throat • inability to urinate • jaundice (yellowing of skin and/or eyes) • painful red eyes	• decreased kidney function • difficulty breathing • injection site swelling • allergic reaction (swelling of face, mouth, and/or tongue) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Infrequent:

• chest pain due to heart trouble • stoppage of heart and lung function • inflammation of the membranes around the spinal cord and brain (possible headache and/or coma) • mental status change • paralysis	• brain damage that may be reversible (possible headache, confusion, seizures, and/or vision loss) • enlarged bowel (possible abdominal pain) • high blood levels of uric acid (possible painful joints and/or kidney failure) • abnormal blood test (possible pancreas inflammation and/or damage)	• liver damage due to blood clots • breakdown of muscle tissue (possible kidney failure) • lung inflammation (possible difficulty breathing) • injection site pain and/or swelling • cytarabine syndrome (bone/chest/muscle pain, painful red eyes, fever, skin rash, and/or fatigue/lack of energy)

Additional side effects seen only in high dose cytarabine:

It is not well known how often the following side effects may occur.

• enlarged heart • decreased brain function affecting movement • coma • nervous system damage (possible seizure and/or coma) • nerve damage (possible numbness, pain, and/or loss of motor function) • personality change • sleepiness • skin peeling • hair loss (partial or total)	• skin rash • stomach and/or small intestine ulcer • abdominal wall inflammation • inflammation of the pancreas (possible abdominal pain) • air-filled cysts in the intestines • decreased blood flow to part of the bowel (possibly causing death of tissue)	• pus-filled areas in the liver • liver damage • damage to the surface of the eye • bleeding in the eye • difficulty breathing • fluid in the lung (possible difficulty breathing) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

When cytarabine is given intrathecally, it may also cause the following side effects:

• decreased brain function (possible paralysis and/or coma) • bladder/bowel dysfunction	• paralysis (possibly of the nerves in the neck and/or both legs) • blindness • double vision	• difficulty swallowing • cough • hoarseness • voice loss

<u>Dexamethasone Side Effects</u>
It is not well known how often the following side effects may occur.

• high blood pressure • irregular/slow heartbeat • sudden stopping of the heart • enlarged heart • heart failure • tearing of the walls of the heart (post-heart attack) • blood vessel inflammation (possible bleeding and/or bruising)	• hair loss (partial or total) • hair growth • sweating • tissue death • Cushing's syndrome (possible weakness, diabetes, and/or bone weakness) • decreased ability to process carbohydrates	• worsening of existing myasthenia gravis (immune response causing muscle weakness) • bruising • abnormal blood test (possible kidney damage) • enlarged liver • abnormal liver tests (possible liver damage)

• blood clots in a vein (possible pain, swelling, and/or redness) • blood clots in the arteries (possible organ damage such as stroke and/or heart attack) • swelling (tissue/abdomen) • dizziness • shock • fainting • headache • increased pressure in the skull or between the skull and brain (possible headache, vision changes, and/or mental status changes) • seizure • depression • mood swings • personality changes • euphoria (unusual feelings of happiness or well-being) • difficulty sleeping • fatigue/lack of energy • darkening and/or lightening of the skin • tiny dots on the skin • wound healing problems • skin rash, redness, and/or dryness • fragile and/or thinning skin • skin tests (such as for TB) may not be accurate • stretch marks • hives • acne	• high blood sugar (possible diabetes) • diabetes • decreased production of adrenal hormones (possible weakness and/or low blood pressure) • body-wide loss of proteins (possible weakness and/or swelling) • changes in body salts such as sodium, potassium, and/or magnesium (possible fatigue and/or weakness) • build-up of fat in abnormal areas • pituitary gland failure (possible hormone imbalance) • weight gain • increased appetite • digestive system bleeding • esophageal sore • hole in the intestines (possibly leaking contents into the abdomen) • nausea • itching near the anus • inflammation of the pancreas (possible abdominal pain) • stomach ulcer • changes to the menstrual cycle • problems with production of sperm	• weakness • inflammation of nerves (possible pain and/or loss of motor or sensory function) • joint disease/pain • pain or loss of function of the hips or shoulders due to bone death • broken bones • loss of muscle • muscle damage causing weakness • nerve damage (loss of motor or sensory function) • abnormal sensation (such as pins and needles) • tendon tear • collapse of bones in the spine • bulging eye • increased pressure in the eye (possible vision loss, pain, and/or blurry vision) • cataracts (clouding of the lens of the eye) • hiccups • fluid in the lung (possible difficulty breathing) • allergic reaction that may be life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure) • infection

Dexamethasone may cause you to develop another type of cancer.

Methotrexate Side Effects

Exact frequency unknown but occurring in more than 10% of patients:

• inflammation of the membrane around the spinal cord and brain (possible headache, vomiting, and fever) • nerve damage (loss of motor or sensory function) • paralysis of nerves controlling the head and neck	• coma • skin redness • high blood levels of uric acid (possible painful joints and/or kidney failure) • low sperm count • mouth blisters/sores • swollen tongue • gum disease • nausea • vomiting	• diarrhea • hole in the intestines (possibly leaking contents into the abdomen) • low blood cell counts (red, white, and platelets) • kidney failure • build-up of bodily waste products in the blood (possible kidney damage) • sore throat

Exact frequency unknown but occurring in between 1 and 10% of patients:

• blood vessel inflammation (possible bleeding and/or bruising) • dizziness • fatigue/lack of energy • decreased brain function (possible paralysis and/or coma) • fever • chills • hair loss (partial or total) • skin rash and/or itching • skin sensitivity to sunlight or lamps	• lightening or darkening of skin • diabetes • bladder inflammation (possible pain and/or urge to urinate) • liver damage due to scarring • scarring of a vein to the liver (possible liver damage) • abnormal liver test (possible live damage)	• joint pain • blurry vision • decreased kidney function • abnormal blood test (possible muscle disorders) • decreased urine output • lung inflammation (possible difficulty breathing) • cough • infection

Rare but serious (occurring in less than 1% of patients)

• chest pain • low blood pressure (possible dizziness/fainting) • heart attack	• very severe blistering skin disease (with ulcers of the skin and digestive tract) • very severe blistering skin disease	• broken bone(s) • paralysis • increase in white blood cells • liver failure

• irregular heartbeat • stroke • blood clots in an artery (possible organ damage such as stroke and/or heart attack) • blood clots in a vein (possible pain, swelling, and/or redness) • blood clots in the brain • inflammation of and/or build-up of fluid in the tissue around the heart (possible chest pain) • decreased blood supply to the heart • brain damage that may be reversible (possible headache, confusion, seizures, and/or vision loss) • fainting • seizure • inability to speak • difficulty forming or speaking words • weakness on one side of the body	(loss of large portion of skin) • shedding and scaling of the skin (possible fatal loss of bodily fluids) • red, dry, scaly patches of thickened skin (psoriasis) • allergic skin reaction • low blood level of albumin (possible swelling, weakness, and/or fatigue) • decreased supply of blood to the abdomen • abdominal pain • vomiting of blood • tarry or coffee ground-like blood in the stool • inflammation of the pancreas (possible abdominal pain) • blood in the urine • abnormal hole inside the nose • bone destruction and soft tissue death of tissue (with radiotherapy)	• liver damage due to inflammation • blindness • blood clot inside the eye (possible blindness) • difficulty breathing • failure to breathe • lung damage (possible difficulty breathing) • blood clots in the lung (possible failure to breathe) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure) • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

Methotrexate may rarely cause you to develop another type of cancer (such as lymphoma, a type of lymph node cancer).

Frequency Unknown

• birth defects	• miscarriage

Liposomal Vincristine Side Effects

Likely (occurring in more than 20% of patients)

• fever • fatigue • difficulty sleeping • constipation	• nausea • diarrhea • loss of appetite	• low red blood cell count • nerve damage (loss of sensory function and/or affecting movement)

Common (occurring in 3-20% of patients)

• low blood pressure (possible dizziness/fainting) • sudden stopping of the heart • mental status changes • paralysis of the intestines	• low blood count (white, platelets) • bacteria in the blood • abnormal liver test (possible liver damage) • weakness • pain (such as abdominal pain)	• nerve damage (possible numbness, pain, and/or loss of motor function) • difficulty breathing • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

At this time, there are no known serious side effects that occur in **fewer than 3% of patients**.

It is not known how often the following side effects may occur:

• liver damage	• breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

Rituximab Side Effects

Common (occurring in more than 20% of patients)

• fever • fatigue • chills	• nausea • low blood cell counts (red, white, platelet) • weakness	• nerve damage (loss of motor or sensory function) • infection

Rituximab may commonly cause infusion reactions such as difficulty breathing and/or tissue swelling. In some cases, life-threatening reactions such as sudden stopping of the heart and/or shock caused by heart damage may occur. It is not known how often these more serious reactions may occur.

Because rituximab is a mouse antibody that has been changed to make it similar to a human antibody, treatment with rituximab may commonly cause the body to make human antibodies to the mouse-based antibody. These antibodies are called HAMA or HACA. The potential response of your body to rituximab may lead to decreasing the effectiveness of mouse-based antibody

therapies for you in the future. If you receive other drugs in the future that contain mouse proteins, you could develop an allergic reaction to those drugs.

Occasional (occurring in 3-20% of patients)

• high blood pressure • low blood pressure (possible dizziness/fainting) • swelling (arm/leg/ tissue) • flushing • anxiety • headache • difficulty sleeping • dizziness • skin rash	• itching • night sweats • hives • high blood sugar (possible diabetes) • diarrhea • abdominal pain • weight gain • vomiting • upset stomach	• abnormal liver and/or bone tests (possible liver damage) • pain (back/joint/muscle) • muscle spasms • difficulty breathing (possibly due to narrowing of the airways) • cough • runny nose • nosebleed • sore throat

Rare but serious (occurring in fewer than 3% of patients)

• sudden stopping of the heart • fast and/or irregular heartbeat • chest pain due to heart trouble • heart failure • heart attack • blood vessel inflammation (possible bleeding, bruising, and/or rash) • shock caused by heart damage • inflammation of the brain and spinal cord (possible altered consciousness) • progressive multifocal leukoencephalopathy (PML – a disease with brain damage that may likely result in paralysis and/or coma, which may be permanent, or death) • brain injury that may be reversible (possible headache, confusion, seizures, and/or vision loss)	• severe painful blisters • severe skin rash • very severe blistering skin disease (with ulcers of the skin and digestive tract) • very severe blistering skin disease (loss of large portion of skin) • blockage and/or hole in the intestines (possibly leaking contents into the abdomen) • anemia due to destruction of red blood cells • thick blood (possible blockage of blood flow) • condition that looks like lupus (an immune system disease) • immune system reaction (possible organ damage) • liver damage/failure • muscle inflammation and weakness • abnormal sensation (such as pins and needles)	• kidney damage/failure • inflammation inside the eye and/or of an eye nerve (possible vision problems) • bronchiolitis obliterans (damage of the small airways with difficulty breathing) • lung inflammation (possible difficulty breathing) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • worsening of Kaposi's sarcoma • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure. The risk of hepatitis B virus flaring up may continue for several months after you stop taking rituximab. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor right away. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.

Rituximab may also cause other viruses to reactivate. This includes JC virus (PML), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C.

Talk to the study doctor before receiving any vaccines (for example, vaccines for measles, mumps, rubella, or polio). Receiving a vaccine while taking rituximab may increase the risk of serious infection or make the vaccine less effective.

Chemotherapy injected directly into the spinal fluid may cause nausea, vomiting, headaches, and/or irritation of the lining of the spinal cord (chemical meningitis). It may lead to infection. If an Ommaya catheter is used for the intrathecal therapy, it may leak, bleed, and/or become infected. An Ommaya catheter may lead to a change in the flow of the spinal fluid.

Using **the study drugs together** may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Having **bone marrow aspirations** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the collection. An allergic reaction to the anesthetic may occur. A scar may form at the collection site.

You may experience pain, bleeding, and/or bruising from the **blood draws**. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

4a. Because taking part in this study can result in risks to an unborn or breastfeeding baby, you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study if you are sexually active.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant will result in your removal from this study.

5. POTENTIAL BENEFITS

This treatment may help to control the disease. Future patients may benefit from what is learned in this study. There may be no benefits for you in this study.

6. ALTERNATIVE PROCEDURES OR TREATMENTS

You may choose not to take part in this study. You may choose to receive other standard therapies, such as chemotherapy combinations with vincristine, prednisone, asparaginase, and/or cyclophosphamide. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

Additional Information

7. You may ask the study chair any questions you have about this study. You may contact the study chair, Dr. Elias Jabbour, at 713-792-7543. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-2933 with any questions that have to do with this study or your rights as a study participant.

8. Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

9. This study or your participation in it may be changed or stopped at any time by the study chair, Spectrum Pharmaceuticals, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP - a regulatory agency that oversees research in humans), or the IRB of MD Anderson.

10. You will be informed of any new findings that might affect your willingness to continue taking part in the study.

11. MD Anderson may benefit from your participation and/or what is learned in this study.

12. This study is supported by: Spectrum Pharmaceuticals.
13. The MD Anderson Conflict of Interest policy states that MD Anderson employees may not serve as the study chair or co-chair on a research study if they have received funds that are greater than the amount allowed by the policy or own stock in the sponsoring or supporting companies.

    The MD Anderson Conflict of Interest policy and the IRB require that you be told about significant financial relationships that the study staff and MD Anderson officials may have with the study sponsor(s).

    At this time, no significant financial relationships with the study sponsor(s) have been disclosed by any of the study staff.

14. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s). If you have any questions about this, you may call the IRB at 713-792-2933.

STUDY COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or Spectrum Pharmaceuticals for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs, including hospitalization, nausea, vomiting, low blood cell counts, and dehydration. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research. You will receive no compensation for taking part in this study.

Authorization for Use and Disclosure of Protected Health Information:

A. During the course of this study, the research team at MD Anderson will be collecting and using your protected health information. This information may include personal identifying information about you (such as your name, race, date of birth, gender, city, and zip code), your medical history, study schedule, and the results of any of your tests, therapies, and/or procedures. The purpose of collecting and sharing this information is to learn about how the study procedures may affect the disease and any study-related side effects. Your doctor and the research team may share your study information with the parties named in Section D below.

B. Signing this consent and authorization form is optional. However, if you refuse to provide your authorization to use and disclose your protected health information for this study, you will not be able to participate in this research project.

C. MD Anderson will take appropriate steps to keep your protected health information private when possible, and it will be protected according to state and federal law. However, there is no guarantee that your information will remain confidential, and it may be re-disclosed at some point. Federal agencies (such as the FDA, OHRP, or National Cancer Institute [NCI]), Spectrum Pharmaceuticals, and the IRB of MD Anderson might view or receive your record in order to collect data and/or meet legal, ethical, research, and safety-related obligations. In some situations, the FDA could be required to reveal the names of participants.

D. Your protected health information may be shared with the following parties:

- Spectrum Pharmaceuticals (and/or any future sponsors of the study)
- Federal agencies that require reporting of clinical study data (such as the FDA, NCI, and OHRP)
- The IRB of MD Anderson
- Officials of MD Anderson
- Clinical study monitors who verify the accuracy of the information
- Individuals with medical backgrounds who determine the effect that the treatment procedures may have on the disease
- Individuals who put all the study information together in report form

E. There is no expiration date for the use of your protected health information. You may withdraw your authorization to share your protected health information at any time in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP). You may contact the IRB Staff at 713-792-2933 with questions about how to find the NPP. If you withdraw your authorization, you will be removed from the study, and the study chair and staff will no longer use or disclose your protected health information in connection with this study, unless the study chair or staff needs to use or disclose some of your research-related personal health information to preserve the scientific value of the study. Data collected about you up to the time you withdrew will be used and included in the data analysis. The parties listed in Section D above may use and disclose any study data that were collected before you canceled your authorization.

F. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF PARTICIPANT _____ DATE _____

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF LAR _____ DATE _____

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

RELATIONSHIP TO PARTICIPANT _____

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol **2008-0598**.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) _____ DATE _____

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

PERSON OBTAINING CONSENT

I have discussed this clinical research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF STUDY CHAIR OR PERSON AUTHORIZED TO OBTAIN CONSENT _____ DATE _____

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into _____ and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

NAME OF TRANSLATOR	SIGNATURE OF TRANSLATOR	DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION (OTHER THAN TRANSLATOR, PARENT/GUARDIAN, OR STUDY CHAIR)	DATE