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Protocol Page

Phase 2 Study of the Activity and Safety of Fludarabine, Cyclophosphamide, and Mitoxantrone plus Rituximab (FCM-R) with Pegfilgrastim (Neulasta) as Frontline Therapy for Patients < 70 Years with Chronic Lymphocytic Leukemia
2005-0106

Core Protocol Information

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| Short Title | Phase 2 Study of FCM-R (Fludarabine, Cyclophosphamide, Mitoxantrone, Rituximab) in Previously Untreated Patients with CLL < 70 Years |
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Which Committee will review this protocol?

The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary

- To determine the clinical response rate (combined morphological [NCI WG criteria] and flow cytometry criteria) following treatment with FCM-R in patients with previously untreated CLL.
- 1.2 Secondary
- To determine the molecular response rate (PCR for IgH rearrangements) following treatment with FCM-R in patients with previously untreated CLL.
- To determine the time to treatment failure.
- To determine the toxicity profile of FCM-R.

2.0 Background

2.1 Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the United States and Western Hemisphere. Nearly two-thirds of patients with CLL are over 60 years of age, and the prevalence of this disease should parallel the steady increase in the population over 50 years of age. Interest in newer therapeutic agents has been poor until recently due partly to the usual advanced age of patients and often indolent course of disease. However, the natural history is diverse. Patients with lymphocytosis only (Rai stage 0) have a median survival in excess of 10 years; those with evidence of marrow failure manifested by anemia (Rai stage III) or thrombocytopenia (Rai stage IV) have a median survival in excess of only 2 years. The National Cancer Institute Working Group on CLL has described clinical features of "active disease" which should be helpful in the decision to treat: 1) weight loss of > 10% body weight over the past 6 months; 2) fever or night sweats in the absence of infection; 3) extreme fatigue; 4) worsening anemia or thrombocytopenia; 5) massive (> 6cm below the left costal margin) or progressive splenomegaly; 6) massive (> 10cm in the longest diameter) or progressive lymphadenopathy; 7) progressive lymphocytosis with rapid lymphocyte doubling time; 8) marked hypogammaglobulinemia or paraproteinemia [1].

The mainstay of therapy has been systemic chemotherapy consisting usually of an alkylator and a corticosteroid. Chlorambucil plus prednisone has been the standard initial therapy with response rates from 40-77%. Fewer than 15% of these responses have been complete [2-6]. Therapy in patients who are refractory to alkylating agents is unsatisfactory. The response rates are substantially lower (approximately 30%) with rare complete responses [3, 7-9].

Fludarabine has shown marked activity in several indolent lymphoproliferative disorders, including CLL, low-grade lymphoma, macroglobulinemia, and prolymphocytic leukemia [10-14]. Fludarabine administration in previously treated CLL patients has resulted in a 13% complete response rate and 44% partial response rate [10]. Fludarabine has also been given to patients with previously untreated CLL, resulting in even higher response rates with 33% complete response and 50% partial response [11].

Despite attainment of clinical complete response, most patients experience a recurrence at a median of approximately 2 years [15]. This is likely related to the fact that most patients in complete remission have residual disease that can be assessed by several parameters. In previously untreated patients, 55% of CR patients have residual nodules on bone marrow biopsy (nPR). At 2 years, 87% of CR patients are progression-free, versus 55% of nCR patients [15].

Cyclophosphamide has been combined with vincristine (VCR) and prednisone (COP) to treat

lymphoproliferative disorders. Liepman and Votaw first reported on this combination to treat CLL in 1978. Thirty-six patients received this regimen, 23 were previously untreated. The response rate was 72%; 18 of 23 (78%) previously untreated patients responded; 8 of 13 (62%) patients previously receiving chlorambucil responded to COP [16]. Oken and Kaplan treated 18 patients with CLL with CVP (cyclophosphamide 800mg/m² i.v. on day 1 or 400mg/m² orally for 5 days, VCR 2mg i.v. on day 1 and prednisone 60-100mg/m² on days 1-5). All patients were previously treated and 17 of 18 were refractory to chlorambucil. The response rate was 44% [17].

Two randomized trials have been performed. The French Cooperative Group on CLL randomized 291 patients to daily chlorambucil (0.1 mg/kg) or COP, where the cyclophosphamide dose is 300mg/m² orally on days 1-5. The response rate with chlorambucil was 59%, and with COP was 61% [18]. ECOG randomized the same COP regimen versus chlorambucil (30mg/m² orally day 1) and prednisone (80mg orally days 1-5). The response rate for COP was 82% and 72% for chlorambucil and prednisone. Median duration of response and survival were also similar [19]. In all these studies, toxicity was minimal and generally related to myelosuppression in a significantly immunocompromised group. However, VCR in CLL is questionable with two single agent trials reporting no activity in a small number of patients [20].

Fludarabine and cyclophosphamide (FC) has now been used in 128 patients with CLL at MDACC [21]. Thirty-four of these patients received FC as initial therapy. FC produced 80% overall response rate in all patients not refractory to fludarabine at the start of therapy as well as a 38% response rate in patients who were refractory to fludarabine. The CR rate was 35% in previously untreated patients, which was not significantly different from the CR rate in historical control patients treated with single-agent fludarabine. However, residual disease assessed by flow cytometry occurred in only 8% of previously untreated patients achieving CR, and median time to progression has not been reached after a median follow up of 41 months. The FC combination thus seems to have a significant advantage over single-agent fludarabine in the salvage setting. Although the CR rate was not increased in previously untreated patients, residual disease detected by flow cytometry was rare and remission durations seemed to be prolonged in this subset.

2.2 Monoclonal Antibodies in CLL

Monoclonal antibodies have expanded the therapeutic possibilities for patients with lymphoproliferative disorders. Rituximab has been studied extensively in low-grade lymphomas. One hundred sixty-six patients with advanced stage low-grade or follicular lymphoma were enrolled in the pivotal phase II portion of the study [22]. Rituximab was administered at a dose level of 375mg/m² once weekly for four weeks. There were 105 males and 61 females with a median age of 58 years (range, 22-79) and 40% of patients were over 60 years of age. All patients had relapsed with a median of 3 (range, 1-7) prior chemotherapy regimens. Of the 166 patients, 161 completed all four infusions. Side effects (chills, fever, nausea, vomiting, headaches) were usually mild to moderate and associated with the first Rituximab infusion. The mean half-life of free (serum) antibody was 1.8 days following the first dose and 6.2 days following the fourth infusion. Quantifiable immunoreactivity (HAMA or HACA) was not observed. There were 80 responders (10 CRs and 70 PRs); a response rate of 48% (95% CI: 41-56%). The median time to onset of response was 50 days (range, 21-288 days). The median duration of response has not been reached after 9.2 months (range, 1.9 to 18.8+ months). The response rate in 23 patients previously treated with ABMT was 78% compared with a 43% response rate in patients who had not undergone ABMT. The response rate in patients with SLL (WDLL), the tissue counterpart of CLL, was only 12%.

Whereas Rituximab has been studied extensively in low grade lymphoma, fewer studies have been undertaken in CLL, and with less success at standard dose and schedule. To improve response rates, we have undertaken a dose escalation study with all patients receiving rituximab 375mg/m² on the first course of therapy and each week thereafter receiving doses ranging from 500mg/m² up to 2250 mg/m² per day [23]. No unusual toxicity occurred after the first infusion.

The response rate is 41% in 23 of 30 CLL patients evaluated and 50% in all patients treated. Higher doses have a higher response rate. In a similar dose escalation study, rituximab was given at 375mg/m² i.v. three times weekly for 4 weeks [24]. Although dose increases were observed compared to the standard dose of rituximab, dose escalation trials have also highlighted the limitations of that approach: 1) financial considerations; 2) limited increase in response rates with moderately elevated doses; 3) dependence of response on antigen density and anatomic disease site; and 4) no improvement of responses in fludarabine-refractory patients.

Preclinical studies suggested synergistic activity of rituximab with chemotherapy agents including fludarabine and cyclophosphamide. We have conducted a phase II study of rituximab combined with fludarabine and cyclophosphamide (FCR) for advanced or progressive CLL as well as initial therapy [25, 26]. One hundred and thirty-five previously untreated patients were treated. Using NCI WG criteria, 67% obtained a CR, 14% of the patients achieved a nodular partial remission (nPR), and 14% a partial response (PR). Eight-five (63%) of patients evaluated were able to obtain a flow cytometry remission with < 1% CD5/CD19 co-expressing cells and 41 (55%) of 74 patients tested were able to become PCR negative for immunoglobulin heavy chain rearrangement in their bone marrow. Marrow PCR negativity was more common in those with CR (59%) compared with nPR (44%) and PR (50%) patients. The FCR regimen was well tolerated with grade 3-4 neutropenia being the most common toxicity being present in 56% of courses. The same combination has been used in previously treated patients with CLL. In a preliminary analysis, of 102 patients 23% achieved CR, 14% nPR, and 36% for an overall response rate of 72%. Five of 13 patients (38%) in CR had undetectable IgH rearrangements by PCR. These results and others confirm that chemo-immunotherapy combinations are very active and appear to achieve far superior results compared to chemotherapy or monoclonal antibody therapy alone.

2.3 Mitoxantrone in the treatment of CLL

Mitoxantrone has been used frequently in patients with lymphoproliferative disorders including CLL. We have previously conducted a phase II study of fludarabine plus mitoxantrone in 88 patients with CLL [27]. Fludarabine was administered at 30mg/m² i.v. daily for 3 days and mitoxantrone at 10mg/m² on day 1. The OR was 66%. The response was 83% in previously untreated patients, 87% in patients previously treated with alkylating agents, 50% in patients whose disease was not refractory to fludarabine at the start of therapy, and 25% in patients with fludarabine-refractory CLL. The median progression-free survival was 24 months for all patients and 34 months for previously untreated patients. Experience with FC and mitoxantrone has been published in relapsed and refractory CLL [28]. Of 60 patients, 37 received fludarabine at 25mg/m² i.v. day 1-3, cyclophosphamide at 200mg/m² i.v. day 1-3, and mitoxantrone 6mg/m² i.v. on day 1, at 4-week intervals for up to six courses. Twenty-three patients received FCM with cyclophosphamide at 600mg/m² i.v. and mitoxantrone 8mg/m² i.v. Overall, 50% of the patients achieved CR including 10 cases with molecular responses as assessed by PCR testing. Twenty-eight percent achieved PR for an overall response of 78%. FCM thus induced a high CR rate, including a significant number of patients with molecular responses in patients with previously treated CLL.

Given the positive experience with rituximab chemotherapy combinations, we propose to combine FCM with rituximab in patients with previously untreated CLL. There is extensive experience with these drugs in CLL although not with this particular combination. The FCM-R regimen is being explored in other low-grade lymphoproliferative disorders and mantle cell lymphoma. We do not expect any unusual toxicities. We propose this protocol for younger patients with good prognosis markers (beta-2-microglobulin <= 4 mg/dL) for the following reasons: i) chemoimmunotherapy results are more favorable in this age group than in patients over age 70 for whom alternative programs are being developed; ii) beta-2-microglobulin has emerged as an important prognostic marker in our FCR experience; iii) the addition of mitoxantrone to FCR is not a radical change in the overall rationale of FCR and good prognosis patients may benefit more from it than poor prognosis patients who again demonstrate an inferior

response and survival to the FCR; and iv) alternative programs are being developed for poor prognosis patients (based on beta-2-microglobulin levels).

2.4 Pegfilgrastim

Pegfilgrastim (Neulasta™) is a covalent conjugate of recombinant methionyl human G-CSF(Filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a lineage-specific hematopoietic growth factor that preferentially stimulates the growth and differentiation of neutrophil precursors and the function of mature neutrophils.

Pegfilgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

For information on preclinical and toxicology studies, please refer to the Investigator's Brochure.

Pegfilgrastim was evaluated in two randomized, double-blind, active-control studies, using doxorubicin 60 mg/m² and docetaxel 75 mg/m² administered every 21 days for up to 4 cycles of the treatment of high risk and metastatic breast cancer. Study 1 investigated the utility of a fixed dose of pegfilgrastim. Study 2 used a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (ANC < 0.5 x 10⁹/L) with a mean duration of 5 to 7 days, and a 30 to 40% incidence of febrile neutropenia.

In study 1, 157 subjects were randomized to receive a single SC dose of 6 mg of pegfilgrastim on day 2 of each chemotherapy cycle or filgrastim 5 mg/kg/day SC beginning on day 2 of each cycle. In study 2, 310 subjects were randomized to receive a single SC injection of pegfilgrastim at 100 mg/kg on day 2 or filgrastim 5 mg/kg/day SC beginning on day 2 of each cycle of chemotherapy. Both studies met the primary objective of demonstrating that the mean days of severe neutropenia (ANC < 0.5 x 10⁹/L) of pegfilgrastim-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The rates of febrile neutropenia in the 2 studies were comparable for pegfilgrastim and filgrastim (in the range of 10% to 20%). Other secondary endpoints included days of severe neutropenia in cycles 2 to 4, the depth of ANC nadir in cycles 1 to 4, and the time to ANC recovery after nadir. In both studies, the results for the secondary endpoints were similar between the two treatment groups.

Pegfilgrastim 6 mg will be administered subcutaneously as a single injection once per cycle following the end of chemotherapy.

3.0 Background Drug Information

3.1 Fludarabine

3.1.1 Supply: Sterile, 50 mg prepared as a white lyophilized powder with sodium hydroxide to adjust pH.

3.1.2 Solution Preparation: Fludarabine for injection should be prepared for parenteral use by aseptically adding Sterile Water for Injection USP. When reconstituted with 2mL of Sterile Water for Injection, USP, the solid cake should fully dissolve in 15 seconds or less; each mL of the resulting solution will contain 25 mg of fludarabine phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2 – 8.2. In clinical studies, the product has been diluted in 100 cc or 125 cc of 5% Dextrose Injection USP or 0.9% Sodium Chloride USP.

Reconstituted Fludara for Injection contains no antimicrobial preservative and thus should be used within 8 hours of reconstitution. Care must be taken to assure the sterility of prepared solutions. Parenteral drug products should be inspected visually for particulate matter and

discoloration prior to administration.

3.1.3 **Handling and Disposal:** Procedures for proper handling and disposal should be considered. Consideration should be given to handling and disposal according to guidelines issued for cytotoxic drugs. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Caution should be exercised in the handling and preparation of Fludara for Injection solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution contacts the skin or mucous membrane, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Avoid exposure by inhalation or by direct contact of the skin or mucous membranes.

3.1.4 **Stability:** Fludarabine phosphate is relatively stable in aqueous solution. Over a pH range of approximately 4.5 to 8 in aqueous buffer solutions stored at 65C, approximately 11% decomposition occurred in one day. From this pH profile, the optimum pH was determined to be approximately 7.7. At concentration of 25 mg/ml in distilled water stored at room temperature in normal laboratory light, fludarabine phosphate exhibited less than 20% decomposition in 16 days.

Diluted to concentration of 1 mg/ml in 5% dextrose injection, USP, or in 0.9 sodium chloride injection, USP, less than 3% decomposition occurred in 16 days at room temperature under normal laboratory light.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded eight hours after reconstitution.

3.1.4 **Route of Administration:** Intravenous.

3.2 Cyclophosphamide:

3.2.1 **Formulation:** Cyclophosphamide is available as powder for injection in vials of 100 mg, 200 mg, and 500 mg. Add 5 mL of sterile H2O for injection or normal saline for injection to a 100 mg vial, 10 mL to a 200 mg vial, and 25 mL to a 500 mg vial. The resulting concentrations will be 20 mg/mL. For infusion, cyclophosphamide is diluted further with 100 to 250 mL of D5W or NS and infused as directed.

3.2.2 **Storage:** Vials containing undiluted cyclophosphamide for injection should be stored at room temperature. After mixing, the solution is stable for 24 hours at room temperature and 6 days if refrigerated.

3.3 Mitoxantrone:

3.3.1 **Dosage Forms:** Injection: 2 mg/mL (10 mL, 12.5 mL, 15 mL)

3.3.2 **Administration:** Maximum concentration: 2 mg/mL. Standard IVPB fluid: 100 mL. Maximum IVPB rate: 15 minutes; can be administered as IV push (2-5 minute infusion) if ordered by physician. Room temperature stability: 14 days. Refrigeration stability: 14 days. Special precautions: vascular irritant.

3.3.3 **Route of administration:** intravenous.

3.4 Pegfilgrastim (Neulasta)

3.4.1 **Packaging and Formulation:** Pegfilgrastim 6 mg fixed dose (0.6 mL of a 10 mg/mL solution) will

be presented as a clear, colorless, sterile liquid in a pre-filled staked needle syringe with UltraSafe® Needle Guards. The formulation is 10.0 mg PEGr-metHuG-CSF per mL of 10 mM Sodium Acetate, 5% Sorbitol, 0.004% Polysorbate 20, pH 4.0. Each subject box will contain 1 pre-filled syringe.

3.4.2 Storage: Pegfilgrastim must be stored at 5 +/- 3C. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow pegfilgrastim to freeze and do not use if contents freeze in transit or in storage. As the product contains no preservatives, pre-filled syringes are designed for single use only.

3.4.3 Preparation: No preparation is required for administration of pegfilgrastim. Each subject will receive the 6 mg fixed dose pegfilgrastim. The entire contents of the 0.6 mL pre-filled syringe should be administered irrespective of the subject's actual weight.

3.5 Rituximab

Rituximab is a highly purified, 1328-amino acid antibody with an approximate molecular mass of 145 kD. The chimeric mouse/human anti-CD20 antibody is a glycosylated IgG1 immunoglobulin containing murine light and heavy chain variable regions and human 1 heavy chain and light chain constant regions.

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

4.0 Patient Eligibility

Inclusion:

4.1 Untreated CLL, CLL/PLL, or SLL (small lymphocytic lymphoma) with indication for therapy (Indications for therapy include at least one of the following): i) one or more disease-related symptoms [fever, night sweats, weight loss, pronounced fatigue]; ii) advanced stage disease (Rai stage >/= 3 or Binet stage C); iii) autoimmune anemia and/or thrombocytopenia that is unresponsive to other therapies; iv) massive or progressive hepatomegaly and/or splenomegaly and/or lymphadenopathy; iv) recurrent infections; v) rapid lymphocyte doubling time of < 6 months).

4.2 Age < 70 years.

4.3 Adequate liver function (total bilirubin </= 2.5 mg/dL, SGPT </= 4 x ULN) and renal function (serum creatinine </= 2.0 mg/dL). Patients with renal or liver dysfunction due to suspected organ infiltration by lymphocytes may be eligible after discussion with the Principal Investigator, but upper limits for creatinine even under these circumstances must be creatinine < 3mg/dL and bilirubin < 6 mg/dL. Patients with Gilbert's syndrome may be entered on study with bilirubin levels </= 4 mg/dL.

4.4 Beta-2-microglobulin </= 4 mg/dL.

4.5 ECOG performance status </= 2.

4.6 Signed informed consent in keeping with the policies of the hospital.

4.7 Male and female patients who are fertile agree to use an effective barrier method of birth control (ie, latex condom, diaphragm, cervical cap, etc.) to avoid pregnancy. Female patients of childbearing potential (non-childbearing is defined as $>/=$ 1 year postmenopausal or surgically sterilized) need a negative serum or urine pregnancy test within 14 days of study enrollment.

Exclusion:

4.8 Active hepatitis B (at least one of the following markers positive: HBsAg, HBeAg, IgM anti-HBc, HBV DNA).

4.9 Concurrent chemotherapy or immunotherapy.

4.10 Pregnant patients.

4.11 History of HIV

4.12 Symptomatic CNS disease

4.13 Symptomatic heart disease (NYHA class $>/=$ 3) or LV ejection fraction $<$ 40% (by MUGA or echocardiogram)

5.0 Treatment Plan

5.1 General

This is a non-randomized, open-label phase 2 study of FCM-R for patients with previously untreated CLL. The doses of FCM and R have been established in earlier and published trials. All drugs are commercially available.

5.2 Treatment Plan

Up to 6 courses can be administered.

Course 1:

| Agent | Dose | Day(s) | Route | Time |
|----------------------|---------------------------|--------|-------|-------------|
| Fludarabine | 25mg/m ² /day | 2,3,4 | i.v. | 5-30 mins. |
| Cyclophosphamide | 250mg/m ² /day | 2,3,4 | i.v. | 5-30 mins. |
| Mitoxantrone | 6mg/m ² /day | 2 | i.v. | 30-60 mins. |
| Rituximab | 375mg/m ² /day | 1 | i.v. | 2-6 hours |
| Pegylated Filgrastim | 6mg | 4 | s.c. | NA |

Courses 2 - 6:

| Agent | Dose | Day(s) | Route | Time |
|----------------------|---------------------------|--------|-------|-------------|
| Fludarabine | 25mg/m ² /day | 1-3 | i.v. | 5-30 mins. |
| Cyclophosphamide | 250mg/m ² /day | 1-3 | i.v. | 5-30 mins. |
| Mitoxantrone | 6mg/m ² /day | 1 | i.v. | 30-60 mins. |
| Rituximab | 500mg/m ² /day | 1 | i.v. | 2-6 hours |
| Pegylated Filgrastim | 6mg | 3 | s.c. | NA |

Cyclophosphamide will be given after the dose of fludarabine, and mitoxantrone after completion of the cyclophosphamide infusion. Rituximab will start before fludarabine. Pegylated filgrastim is given after chemotherapy.

CAUTION: DO NOT ADMINISTER RITUXIMAB AS AN INTRAVENOUS PUSH OR BOLUS !

Rituximab will be given on days 1 at a dose of $375\text{mg}/\text{m}^2$ during course 1 and on day 1 at a dose of $500\text{mg}/\text{m}^2$ during courses 2-6.

Recommended premedication: 500 to 1000 mg of acetaminophen orally and 12.5 to 25 mg of diphenhydramine hydrochloride orally or intravenously to be administered 30 to 60 minutes prior to starting each infusion of Rituximab.

Rituximab may be administered via a peripheral or central intravenous line.

During the Rituximab infusion, the patient's vital signs (blood pressure and pulse) should be monitored every 30 minutes times one hour or until stable and then hourly until the infusion is discontinued. Assessment of temperature and respiration as clinically mandated. Available at the bedside prior to Rituximab administration will be epinephrine for subcutaneous or i.v. injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions.

The initial dose rate at the time of the first Rituximab infusion should be 50 mg/hr for the first hour. If no toxicity is seen, the dose rate may be escalated gradually to a maximum of 400 mg/hour. If the first dose of Rituximab is well tolerated, the starting flow rate for the administration of the subsequent doses may be 100 mg/hour and then increased gradually not to exceed 400 mg/hour.

Rituximab is associated with hypersensitivity reactions (hypotension, bronchospasm, or angioedema), which may respond to adjustments in the infusion rate. Transient fever and rigors may occur. Rituximab should be interrupted for severe reactions and resumed at a lower rate until symptoms have completely resolved. Supportive care such as IV saline, diphenhydramine, and acetaminophen should be available and instituted as clinically mandated. Upon resolution of all side effects and in the judgment of the investigator, the patient's dose may be gradually escalated to a maximum rate of 400 mg/hour.

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of Rituximab. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during Rituximab therapy and should be monitored closely. Consideration should be given to withholding anti-hypertensive medications the day of the first infusion, since transient hypotension may occur.

Rate reductions of up to 50% should occur for: (1) fever $> 38.5^\circ\text{C}$, (2) mild to moderate rigors, (3) mild to moderate mucosal congestion/edema, (4) > 30 mm Hg decrease over baseline in systolic blood pressure, or (5) other reaction according to the judgment of the investigator.

Courses will be repeated every 28 to 42 days (+/- 7 days) depending on recovery of peripheral blood counts and toxicities for a maximum of 6 courses. Patients will be evaluated for response after 3 and 6 courses. Patients will be taken off study after 3 courses for progressive disease, but are otherwise allowed to complete 6 courses.

5.3 Dose adjustments

All previously experienced treatment-related toxicities should have recovered to at least grade 1 (exception: alopecia, lymphopenia, fatigue, weakness, nausea/vomiting that can be controlled with supportive care measures) by the time the next course is started. Dose adjustments (one level reduction, see table below) will be made for any grade 3 treatment-related toxicities during the preceding course (exception: alopecia, lymphopenia, fatigue, weakness, nausea/vomiting that can be controlled with supportive care measures or infusion-related toxicities that may occur with

rituximab).

For patients who started therapy with platelets $\geq 100 \times 10^9/L$ and an ANC $\geq 1 \times 10^9/L$, the platelet count should be $\geq 60 \times 10^9/L$ and/or the ANC $\geq 1 \times 10^9/L$ prior to continuation. For patients whose platelets are $< 100 \times 10^9/L$ or ANC $< 1 \times 10^9/L$ at the start of therapy, blood counts should at least have recovered to within 20% of pretreatment baseline levels prior to starting the next course. If recovery of the platelet count or ANC either to the level of prior to therapy or the parameters above exceeds 42 days, the dose will be decreased by 1 level.

Dose Levels (for courses 2 to 6):

| | 0 | -1 | -2 |
|------------------|----------------------------------|----------------------------------|----------------------------------|
| Fludarabine | 25 mg/m ² daily x 3d | 20 mg/m ² daily x 3d | 20 mg/m ² daily x 3d |
| Cyclophosphamide | 250 mg/m ² daily x 3d | 200 mg/m ² daily x 3d | 200 mg/m ² daily x 3d |
| Mitoxantrone | 6 mg/m ² daily x 1d | 6 mg/m ² daily x 1d | 4.5 mg/m ² daily x 1d |
| Rituximab | 500 mg/m ² daily x 1d | 500 mg/m ² daily x 1d | 500 mg/m ² daily x 1d |

No dose escalations are allowed.

Recommended dose reductions of fludarabine in patients with impaired renal function (applies to all courses):

Cl_{cr} 30 to 70 mL/min: reduce dose by 25%

$\text{Cl}_{\text{cr}} < 30$ mL/min: administration of fludarabine not recommended.

If subsequent courses cannot be administered within 3 weeks following day 42 of therapy because of treatment-related toxicities, doses should be reduced by at least one level regardless of recovery of these toxicities to grade 1.

Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation.

5.4 Concomitant Medications/Therapy

Necessary supportive measures for optimal medical care will be given throughout the study as determined by the treating physician and the patient's medical need. No concomitant chemotherapy, immunotherapy, or therapy with other monoclonal antibodies except for rituximab will be allowed during the study. Investigational agents that are not used for the treatment of the leukemia per se (e.g. anti-infective prophylaxis or therapy) will be allowed.

Use of erythropoietin is at the discretion of the treating physician and is permitted if judged in the patient's best medical interest. Use of G-CSF or GM-CSF should be discussed with the principal investigator.

Prophylactic antibiotics and antiviral agents are recommended (e.g. trimethoprim sulfamethoxazole, valacyclovir); however, the use of these or other drugs will be left to the treating physician's discretion.

5.5 Expected adverse events from study drugs

All drugs individually and possibly more so in combination may cause myelosuppression which may be associated with bleeding, bruising, fatigue, or shortness of breath. Transfusion of blood

products may become necessary.

5.5.1 Rituximab:

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, and mild hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate. Other adverse events included neutropenia, thrombocytopenia, asthenia, other hematologic events, cardiac and cardiopulmonary events, and tumor lysis syndrome.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported.

In addition, there have been a limited number of postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).

Cardiac Events: Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

Cardiopulmonary Events: In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred (4-7/10,000 patients or 0.04-0.07%). Nearly all fatal infusion-related events occurred in association with the first infusion.

Tumor Lysis Syndrome: Although rare, tumor lysis syndrome has been reported in postmarketing studies and is characterized in patients with a high number of circulating malignant cells (>25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

Hepatitis B Reactivation: Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

Renal Events: Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases has lead to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm²) or high tumor burden who experience tumor lysis syndrome.

Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic

epidermal necrolysis, have been reported rarely in patients treated with rituximab. Paraneoplastic pemphigus has been reported very rarely in NHL and CLL patients undergoing chemotherapy plus rituximab treatment. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

Additional Safety Signals: The following immune serious adverse events have been reported to occur rarely (<0.1%) in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphigus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis

See the rituximab Investigator Brochure for additional details regarding safety experience with rituximab.

5.5.2 Cyclophosphamide:

Diarrhea, nausea, vomiting, and/or loss of appetite. Electrolyte abnormalities. Cystitis. Cyclophosphamide may cause a metallic taste immediately after it is given. Mucositis, gastritis, and/or temporary alopecia. It may cause headache, dizziness, stuffy nose, and/or testicular shrinkage. It may also cause loss of menstrual periods and/or allergic reaction.

5.5.3 Fludarabine:

Loss of appetite, fatigue, confusion, numbness, nausea, vomiting, and/or diarrhea. Fatigue and weakness. Vision and/or hearing problems. Neurotoxicity (including seizures and coma). Skin rash, mucositis/stomatitis and/or alopecia. Congestive heart failure, pulmonary fibrosis, hematuria. Hepatotoxicity. Nephrotoxicity. Sterility (may be permanent).

5.5.4 Mitoxantrone:

Loss of appetite, fatigue, weakness, nausea, vomiting, and/or diarrhea. Mucositis/stomatitis. Alopecia. Hepatotoxicity. Nephrotoxicity. Sterility (may be permanent).

5.5.5 Pegfigrastim:

Pain, burning, swelling, bleeding/bruising, or infection at the injection site. It may generate bone pain for which pain medications are sometimes required.

6.0 Pretreatment evaluation

| Procedure | Comments | Schedule |
|----------------------|--|-------------------------------|
| Informed consent | Obtain standard informed consent approved by IRB | Within 14 days of study start |
| Medical History | Includes history of present illness, prior cancer history as far as traceable and relevant, and past medical/surgical history as far as relevant | Within 14 days of study start |
| Physical examination | Includes vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status | Within 14 days of study start |

| | | |
|-------------------------|--|--------------------------------------|
| Concomitant medications | Document concomitant medications | Within 14 days of study start |
| Hematology | CBC with differential and platelet count | Within 14 days of study start |
| Biochemistry | Creatinine, uric acid, LDH, total bilirubin, SGPT or SGOT) | Within 14 days of study start |
| Beta-2-microglobulin | | Within 14 days of study start |
| Pregnancy test | Serum or urine | Within 14 day of study start |
| HBV screening | Unless a negative test can be documented within the preceding 6 months | Within 6 months of study start |
| Bone marrow | Aspirate/biopsy including flow cytometry and PCR testing for IgH gene rearrangements | Within 6 months prior to study start |
| MUGA or echocardiogram | Assessment of LV ejection fraction | Within 3 months prior to study start |

7.0 Evaluation During Study

| Procedure | Comments | Schedule |
|----------------------|---|---|
| Physical examination | Includes vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status | Prior to each cycle within 3-5 days. Following 3rd and 6th course, and every 6 months (+/- 2 months) as long as on study thereafter. |
| Hematology | CBC with differential and platelet count | Every 1 to 2 weeks as long as on therapy, and during 6 monthly follow up visits as long as on study |
| Biochemistry | At least creatinine, total bilirubin, SGPT or SGOT | Every 2 to 4 weeks as long as on therapy, and during 6 monthly follow up visits as long as on study |
| Beta-2-microglobulin | | Following the 3rd and 6th course |
| Bone marrow | Aspirate/biopsy including flow cytometry and PCR testing for IgH gene rearrangements | After 3rd and 6th course. No marrow is necessary at the end of therapy if non-response or progressive disease can be diagnosed from peripheral blood tests. |

Upon completion of therapy (maximum of 6 courses), patients will return to MDACC every 6 to 12 (+/- 3) months thereafter for as long as on study. Each visit will include a CBC with differential and platelet count, and at least the parts of the SMA-12 as specified in Table 7.0. Bone marrow aspirate/biopsy will be performed as judged indicated by the treating physician or Principal Investigator.

8.0 Criteria for Response

(as per NCI Working Group Criteria)

8.1 Complete Remission (CR):

- Normal physical examination (including nodes, liver, spleen).
- No constitutional symptoms (B-symptoms absent).
- Peripheral blood: Absolute lymphocyte count (ALC) $</= 4 \times 10^9/L$ with Hb $> 11 \text{ g/dL}$, absolute neutrophil count (ANC) $>/= 1.5 \times 10^9/L$, and platelet count $> 100 \times 10^9/L$.
- Bone marrow: $< 30\%$ lymphocytes on aspirate with no evidence of disease on biopsy. [CRu (CR/unconfirmed): increased number or size of lymphoid aggregates without cytologic or architectural atypia].
- Other disease sites: Disappearance of all palpable lymph nodes, spleen and liver without the appearance of new lesions.

8.2 Partial Remission (PR):

- Peripheral blood: ALC reduced by 50%, with either Hb $> 11 \text{ g/dL}$ or 50% improvement in deviation from normal, or ANC $>/= 1.5 \times 10^9/L$ or 50% improvement in deviation from normal, or platelet count $> 100 \times 10^9/L$ or 50% improvement in deviation from normal.
- Other disease sites: Reduction in size of 50% of all palpable lymph nodes, spleen, and liver without appearance of new lesions.

8.3 Nodular Partial Response (nPR):

- Peripheral blood: ALC $</= 4 \times 10^9/L$ with Hb $> 11 \text{ g/dL}$, ANC $>/= 1.5 \times 10^9/L$ and platelet count $> 100 \times 10^9/L$.
- Bone marrow: $< 30\%$ lymphocytes on aspirate with lymphoid nodules seen on biopsy.
- Tumor: Disappearance of all palpable lymph nodes, spleen, and liver without the appearance of new lesions.

8.4 Stable Disease (SD):

- Failure to meet criteria for response and failure to meet criteria for disease progression.

8.5 Progressive Disease (PD):

- Peripheral blood: 50% increase in ALC with a level $> 10 \times 10^9/L$ on at least 2 occasions 2 weeks apart.
- Tumor: An increase of a lesion by 50% over the size present at entry on study or for patients who respond, the size at the time of maximum regression and/or the appearance of new areas of malignant disease. Reappearance of bone marrow disease. A deterioration in performance status or increasing symptoms do not constitute disease progression.

8.6 Molecular Response (MR):

- Negative result by PCR testing for IgH gene rearrangements.

9.0 Criteria for Removal from the Study

9.1 Progressive disease.

9.2 Failure to achieve at least stable disease after 3 courses.

9.3 Grade 4 adverse events in the absence of therapeutic benefit.

- 9.4 Investigator thinks that a change of therapy would be in the best interest for the patient.
- 9.5 If the patient has intercurrent, non-leukemia-related illness that would, in the judgment of the investigator, affect assessment of clinical status to a significant degree.
- 9.6 Active HBV infection or hepatitis.
- 9.7 Severe or life-threatening anaphylaxis or hypersensitivity reaction.
- 9.8 Patient request.
- 9.9 Patient is non-compliant with protocol requirements.
- 9.10 Subjects who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.
- 9.11 The Principal Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to:
 - If the incidence or severity of adverse events indicates a potential health hazard to patients.
 - If the patient enrollment is unsatisfactory.

10.0 Evaluation of Toxicity

Toxicities will be reported according to NCI CTC Version 3 (NCI-CTCAE). See Appendix B for details.

11.0 Reporting Requirements

See Appendix A and F (Leukemia) for Reporting Requirements

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Genentech Drug Safety any **serious adverse event**, whether **expected** or **unexpected**, regardless of causality to either rituximab. All events meeting these criteria will be reported for the time period beginning with any amount of exposure to rituximab through the protocol-defined follow-up period. Serious criteria, definitions, and guidance for reporting follow.

An **adverse event (AE)** is any untoward medical occurrence in a subject participating in an investigational trial or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Serious adverse events (SAE) are adverse events occurring at any dose which meet one or more of the following **serious criteria**:

- Results in **death** (i.e. the AE caused or lead to death)
- Is **life-threatening** (i.e. the AE placed the subject at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)
- Requires or prolongs inpatient **hospitalization** (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)

- Is **disabling** (i.e. the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)
- Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a subject exposed to the trial drug prior to conception or during pregnancy)
- It does not meet any of the above serious criteria but **may jeopardize the subject and may require medical or surgical intervention** to prevent one of the outcomes listed above

SAEs include any sign, symptom or medical condition that meets any of the above criteria and emerges during rituximab treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy.

Expected adverse events are those adverse events that are **listed** or characterized in the current Investigator Brochure.

Unexpected adverse events are those **not listed** in the current Investigator Brochure or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the Investigator Brochure. For example, under this definition, hepatic necrosis would be unexpected if the Investigator Brochure only referred to elevated hepatic enzymes or hepatitis.

Reporting of Serious Adverse Events Associated with Rituximab

All serious adverse events (SAEs) regardless of causality to rituximab (this applies to both expected and unexpected events) should be recorded on a MedWatch 3500A Form (Appendix J) and faxed to:

Genentech Drug Safety
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4683

AND:

The Principal Investigator of the Study and the IRB

MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch

3500A form

- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above.

Study Drug Relationship:

The investigator will determine which events are associated with the use of the study drugs. For reporting purposes, an AE should be regarded as possibly related to the use of the investigational product if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and rituximab administration; and/or
- There is a biologically plausible mechanism for rituximab causing or contributing to the AE; and
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

12.0 Statistical Considerations

This is a phase II study with an objective of determining the clinical response rate in CLL patients treated with fludarabine, cyclophosphamide, mitoxantrone, and rituximab (FCM-R). Eligible patients will be previously untreated, < 70 years of age and have a favorable Beta-2-microglobulin level of $\leq 4\text{mg/dL}$. The addition of mitoxantrone to the regimen is expected to favorably affect patient response. In addition to the FCM-R regimen, patients will receive Neulasta to shorten the duration of neutropenia and reduce the infection rate.

Patients will receive a maximum of 6 courses of therapy, with courses repeated every 28 – 42 days (± 7 days). The maximum total sample size will be 30 patients, with accrual estimated to be 2-5 per month.

A previous phase II clinical trial of patients with fludarabine, cyclophosphamide, and rituximab (FCR) resulted in an overall response rate at 6 months of approximately 95%. In addition to overall response, flow cytometry was measured at 3 months and at 6 months after the start of treatment. The phase II FCR trial found that patients who maintain a flow cytometry $<1\%$ have better survival than those whose flow cytometry is $\geq 1\%$. Therefore, examining the flow cytometry at 3 months is a useful tool for early assessment of the later outcome of survival.

The method of Thall, Simon, and Estey (1996), will be employed to perform interim efficacy and safety monitoring. The patient outcomes of interest are $F = [\text{patients who have a flow cytometry } < 1\% \text{ at 3 months}]$ and $N = [\text{grade III-IV neutropenia during 3 months after start of treatment}]$. We will denote the probability of F for the patients treated with FCR by $\theta_{S,F}$ and for the experimental therapy, FCM-R patients by $\theta_{E,F}$. Similarly, we will denote the probability of N for the patients treated with FCR by $\theta_{S,N}$ and for experimental FCM-R therapy patients by $\theta_{E,N}$.

Historical data is from a phase II trial of 189 previously untreated patients treated with FCR. (Beta-2-microglobulin levels were not considered in the inclusion/exclusion criteria.) The FCR trial found that 34.4% of the patients had a flow cytometry $< 1\%$ at 3 months and 74.6% of the patients had grade III-IV neutropenia. Thus the historical data suggest the probability of a flow cytometry $<1\%$ at 3 months to be $\theta_{S,F} = 65/189$ (34.4%), and we assume that $\theta_{S,F} \sim \text{beta}(65, 124)$. We assume $\theta_{E,F} \sim \text{beta}(1.37, 2.62)$. This distribution has the same mean (0.344) but a larger variance than the standard therapy counterpart. The data from the FCR trial also suggest an estimate of the probability of grade III-IV neutropenia within the first 3

months to be $\theta_{S,N} = 141/189$ (74.6%) and we assume that $\theta_{S,N} \sim \text{beta}(141/48)$. We assume $\theta_{E,N} \sim \text{beta}(2.98, 1.02)$. This distribution has the same mean (0.746) but a larger variance than the standard therapy counterpart.

The goal of the trial is to achieve an increase in patients with favorable flow cytometry to 50%, an increase of approximately 15%, while not allowing the neutropenia rate to increase. At most 30 patients will be treated. We will begin monitoring after 10 patients have been enrolled and then monitor continuously. However, we will not suspend accrual to wait for patients to be evaluated.

Our monitoring rules for these two endpoints are described below:

Flow Cytometry <1% at 3 months

$$\Pr[\theta_{S,F} + 0.15 < \theta_{E,F} \mid \text{data}] \leq 0.01$$

That is, if at any time during the trial we determine that we have less than a 1% chance of showing that the average rate of patients with flow cytometry <1% at 3 months is at least 15% higher than would be expected on the standard of care (i.e. 35%) we will stop the study. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

$$(\# \text{ of patients with Flow Cytometry } <1\% \text{ at 3 months}) / (\# \text{ patients evaluated})$$

$$\leq 1/11, 2/14, 3/17, 4/20, 5/23, 6/26, 7/29.$$

Grade III-IV Neutropenia

$$\Pr[\theta_{S,N} < \theta_{E,N} \mid \text{data}] \geq 0.99$$

That is, if at any time during the study we determine that there is more than a 99% chance that the average rate of grade III-IV neutropenia is more than would be expected on the standard of care (i.e. 75%) we will stop the study. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

$$(\# \text{ patients with grade III-IV neutropenia}) / (\# \text{ patients evaluated})$$

$$\geq 14/14, 15/15, 16/16, 17/17, 18/18, 19/19, 20/20, 21/22, 22/23, 23/24, 24/25, 25/26, 26/27, 27/29.$$

The operating characteristics of this study design are illustrated in Table 1.

Table 1. Operating Characteristics for Monitoring Rules

| Clinical Scenario | Early Stopping Probability | Achieved Sample Size | | |
|--|----------------------------|----------------------|------|------|
| | | 25th | 50th | 75th |
| | | Percentiles | | |
| Rate of flow cytometry <1% at 3 months is 0.50 Rate of grade III-IV neutropenia is 0.75 | 0.06 | 30 | 30 | 30 |
| Rate of flow cytometry <1% at 3 months is 0.50 Rate of grade III-IV neutropenia is 0.85 | 0.25 | 29 | 30 | 30 |
| Rate of flow cytometry <1% at 3 months is 0.40 Rate of grade III-IV neutropenia is 0.75 | 0.22 | 30 | 30 | 30 |
| Rate of flow cytometry <1% at 3 months is 0.35 Rate of grade III-IV neutropenia is 0.85 | 0.49 | 15 | 30 | 30 |
| | | | | |

| | | | | |
|--|------|----|----|----|
| Rate of flow cytometry <1% at 3 months is 0.25 Rate of grade III-IV neutropenia is 0.85 | 0.81 | 10 | 15 | 24 |
|--|------|----|----|----|

In addition to flow cytometry at 3 months we will also determine the flow cytometry at 6 months and present it along with its corresponding 95% credible interval. The secondary objectives include determining the molecular response rate, time to treatment failure, and toxicity profile of FCM-R. Molecular response rate will be defined as the percentage of patients who have a negative result by PCR testing for IgH gene rearrangements and will be presented along with its corresponding 95% credible interval. Time to treatment failure will be estimated using the Kaplan-Meier estimator. Patients who experience a relapse or die will be considered to be a treatment failure event. Patients who are alive without relapse at their last follow-up will be considered as censored. Finally, descriptive statistics such as frequencies and percentages will be used to summarize the occurrence of any toxicities.

13.0 References

- 1 Cheson BD, et al. Am J Hematol 29: 152, 1988.
- 2 Keller JW, et al. Cancer 58: 1185, 1986.
- 3 Montserrat E, et al. Cancer 56: 2369, 1985.
- 4 Sawitsky A, et al. Blood 50: 1049, 1977.
- 5 Han T, et al. Cancer 31: 502, 1973.
- 6 Idestrom K, et al. Eur J Cancer 18: 1117, 1982.
- 7 Kempin S, et al. Blood 60: 1110, 1982.
- 8 Keating MJ, et al. Leukemia 2: 157, 1988.
- 9 Oken ME, et al. Cancer 40: 855, 1977.
- 10 Keating MJ, et al. Blood 74: 19, 1989.
- 11 Keating MJ, et al. J Clin Oncol 9: 44, 1991.
- 12 Redman J, et al. J Clin Oncol 10: 790, 1992.
- 13 Kantarjian H, et al. Blood 75: 1928, 1990.
- 14 Kantarjian HM, et al. Am J Med 90: 223, 1991.
- 15 Roberston LE, et al. Blood 80: 29, 1992.
- 16 Liepman M, et al. Cancer 41: 1664, 1978.
- 17 Oken MM, et al. Cancer Treat Rep 63: 441, 1979.
- 18 The French Cooperative Group on Chronic Lymphocytic Leukemia. Blood 75: 1422, 1990.
- 19 Raphael B, et al. Cancer Res 23: 613, 1963.
- 20 Desai DV, et al. Cancer 26: 352, 1970.
- 21 O'Brien S, et al. J Clin Oncol 19: 1414, 2001.
- 22 McLaughlin P, et al. J Clin Oncol 16: 2825, 1998.
- 23 O'Brien SM, et al. J Clin Oncol 19: 2165, 2001.
- 24 Byrd JC, et al. J Clin Oncol 19: 2153, 2001.
- 25 Keating MJ, et al. Blood 96: 514a, 2000.
- 26 Garcia-Manero G, et al. Blood 96: 757a, 2000.
- 27 Tsimberidou AM, et al. Cancer 100: 2583, 2004.
- 28 Bosch F, et al. B J Haematol 119: 976, 2002.
29. Thall PF, Simon R, and Estey EH. "New statistical strategy for monitoring safety and efficacy in single-arm clinical trials", Journal of Clinical Oncology, 14(1):296-303 (1996).