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E2903

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

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Addendum #12, 5/10
Addendum #13, 6/10
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Table of Contents

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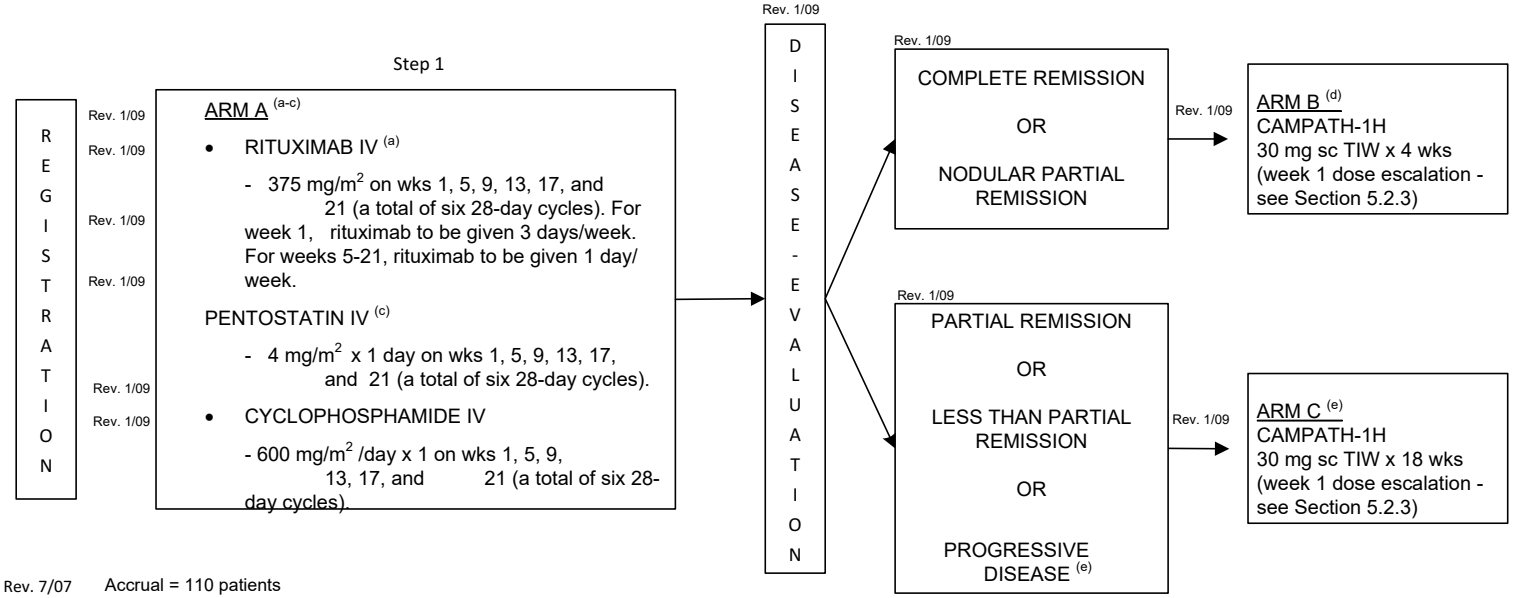
Schema



Rev. 7/07 Accrual = 110 patients

Rev. 1/09 a) The dose of Rituximab (day 1 of week 1) will be 100 mg. The dose of Rituximab will be increased to 375 mg/m^2 on days 3 and again on 5 of week 1 (see Section 5.1.1 to 5.1.3 for rituximab infusion information).

Rev. 1/09 b) See Sections 5.1.1, 5.1.2 and 5.1.4 for details regarding premedication and supportive care.

Rev. 1/09 c) **Serum creatinine will be determined within 14 days of PCR treatment. Serum creatinine must not be > 2mg/dl.**

There are no safe guidelines for administration of pentostatin in patients with a creatinine clearance of < 30ml/min. This will be the minimum clearance for patients on this study therefore, any patients whose clearance is < 30ml/min will discontinue protocol therapy.

See Section 5.1.3.1.1.

Rev. 1/09 d) A 12-week treatment free period following the completion of PCR will elapse before registering to Arm B.

Rev. 1/09 e) Patients who have PR or stable disease when evaluated at the end of PCR have a treatment free period of no less than 2 or no more than 8 weeks before registering to Arm C.

If progressive disease is determined during PCR treatment, the patient is not required to complete 6 cycles of PCR before going on to Arm C CAMPATH-1H for 18 weeks. However, completing a minimum of 2 cycles is required.

Rev. 1/09 f) See Section 5.1.4 and 5.2 for details regarding premedication and support care.

1. Introduction

1.1 Demographics, Natural History and Previous Treatments

B-cell chronic lymphocytic leukemia (CLL) is one of the most common types of leukemia diagnosed in the United States (1). The median age at diagnosis is 60 years old with a 2:1 male to female sex ratio (82,83). Most patients are diagnosed incidentally during routine blood work. For protocol study purposes, the National Cancer Institute (NCI) Working Group on CLL recommends an absolute lymphocyte count threshold value of > 5,000/μl (2). Laboratory diagnosis is achieved through demonstration in the blood smear of "mature" appearing small lymphocytes and immunophenotyping by flow cytometry showing co-expression of CD5 and B cell markers with dim expression of surface immunoglobulin. (2)

Despite the greater than 10-year life expectancy in early stage patients, CLL remains an incurable illness (3-6). Patients progressing onto or diagnosed with more advanced stage CLL have a median survival between 18 months to 3 years. Patients with low-risk, early stage CLL can be followed closely, as there is no survival benefit associated with early intervention (6). With disease symptoms or progressive cytopenias, patients previously were treated with oral alkylating agents with or without prednisone (7-11). Responses to alkylating agents are not durable, and only rarely are associated with morphologic complete remission. With the clinical introduction of the purine analogs (pentostatin, cladribine and fludarabine), treatment of CLL has changed from primary alkylators as front line treatment to purine analogs as front line treatment (12,13).

Rev. 1/14

1.2 Biochemistry of Purine Nucleosides

2-chlorodeoxyadenosine (2-CDA) and pentostatin (deoxycoformycin, DCF), analogs of the naturally occurring deoxypurine nucleoside, deoxyadenosine (dAdo), are effective for the treatment of CLL (13,14,15,24,87). Their primary mechanism of action is promoting the intracellular accumulation of deoxynucleotides by inhibiting the function of adenosine deaminase (ADA), an enzyme that normally degrades deoxypurine nucleotides. Inhibition of adenosine deaminase leads to the accumulation of metabolites inhibiting ribonucleotide reductase. This leads to a depletion of the nucleotide pool with resultant inhibition of DNA synthesis.

1.2.1 Purine Analogs for the Treatment of CLL

Pentostatin, produced by *Streptomyces antibioticus*, was the first purine analog to enter clinical trials in CLL (13,14). Cladribine (15) and fludarabine (16-19) were introduced in the clinic soon after and yielded impressive clinical results in alkylator-refractory CLL. Specifically, treatment with fludarabine yields a 31-57% response rate in alkylator-resistant CLL patients, and a 63-79% response rate in untreated patients (88). The addition of prednisone did not add significant benefit (19). These data have elevated fludarabine to an acceptable front-line therapeutic option in the treatment of symptomatic CLL. Monoallelic p53 gene deletion (detected in 12% of CLL patients) is predictive for nonresponse to therapy with purine analogs (fludarabine) and poor survival (96). Likewise, 17p deletion

(17% of patients) is also associated with resistance to purine analogs, which may be overcome with alemtuzumab therapy (97).

1.2.2 Pentostatin trials were not subjected to extensive schedule optimization despite demonstrated efficacy and lack of significant myelosuppression as compared to other purine analogs. Extensive phase I evaluation was performed (20) and these early studies were notable for remarkable inter-patient variability in toxicity, especially at high doses given for five days. Significant renal, pulmonary, and central nervous system (CNS) toxicity was encountered (21-24). Patients with indolent lymphoid malignancies developed lymphocytopenia at doses producing little toxicity, such as 5 mg/m^2/d for 2 days or 4 mg/m^2 every 1 or 2 weeks. In addition renal insufficiency and poor performance status were predictive of toxicity, even at lower doses of pentostatin (4 mg/m^2). In the phase II studies using 4 mg/m^2 weekly or less frequently, the incidence of mild, reversible creatinine elevation was less than 5%, and no patient developed overt renal failure. CNS toxicity appeared to be schedule-dependent, and could develop with repeated low doses in patients with normal renal function (21). Early clinical trials also revealed adenosine deaminase inhibition resulted in immunosuppression, and may increase the patient's risk of infection during the treatment period (89). Additional side effects include reversible hepatitis, keratoconjunctivitis, nausea, and vomiting (24-26).

1.2.3 In phase II studies, pentostatin has demonstrated activity in patients with relapsed CLL, refractory to alkylating agents. In the largest study, conducted by the Cancer and Leukemia Group B (CALGB) (24), 36 evaluable patients were treated with pentostatin at a dose of 4mg/m^2 three times per week, and then every other week. Among these patients, ten (26%) demonstrated a response: 1 complete response and 9 partial responses. The European Organization for Research and Treatment of Cancer (EORTC) phase II study (25) showed 7 of 26 patients (27%) developed a partial response. In a study of 17 CLL patients at the Royal Marsden Hospital, 35% achieved a response (26). Toxicities documented in these phase II studies with pentostatin show most patients tolerated the treatment well, with mild nausea and vomiting and minor skin rashes being the most common complaint. The most significant toxicity was infection. These included bacterial as well as opportunistic infections that are known to occur in patients receiving purine analog therapy. Virtually all infectious complications occurred within six weeks of initiating therapy with pentostatin. There was worsening of anemia and thrombocytopenia in 23% and 26% of patients, respectively. This was more frequent in those patients who had very low hemoglobin levels and platelet counts when they started treatment. Neither of the two large multicenter trials reported any nephrotoxicity. Three patients (7%) developed grade 3-4 CNS toxicity in the CALGB study, while no such adverse events were reported in the other studies.

1.3 Purine Analogs in Combination Chemotherapy of CLL

Preclinical justification of combining pentostatin and cyclophosphamide comes from a report by Johnson and colleagues (27) where CLL cells were incubated *in vitro* with an alkylating agent and a nucleoside analog. The cyclophosphamide analog, 4-hydroperoxycyclophosphamide (4-HC), which does not require microsomal activation and is converted to the same alkylating agent was utilized. This study demonstrated that combination therapy with 4-HC, pentostatin, and deoxyadenosine produces at least additive cell kill *in vitro*. Preclinical data demonstrated that a combination of a DNA damaging agent (cyclophosphamide) can synergize with the nucleoside analogs fludarabine, pentostatin, or cladribine. Recent reports demonstrated significant activity of a combined pentostatin-cyclophosphamide regimen (28-31). Previously treated patients were required to have "high-risk" or "active intermediate risk" disease. Weiss et al. recently published the results of a Phase II study of pentostatin (4mg/m^2) and cyclophosphamide (600-900 mg/m^2) in twenty-three previously treated patients with chronic lymphocytic leukemia. Therapy was administered every three weeks. The response rate was 77% in fludarabine-refractory patients. There were four complete responses. Grade 3/4 neutropenia and thrombocytopenia were seen in 35% and 30% respectively. There was relative sparing of thrombopoiesis (1/23 patients with a platelet count > 20,000 x 10^6/L required platelets). All patients received filgastrim, sulfamethioxazole/trimethaprim, and acyclovir prophylactically (31). Fludarabine and cyclophosphamide combinations have been developed with similar efficacy (32-34). Previous combinations of fludarabine and chlorambucil demonstrated efficacy but significant toxicity (35,36).

1.4 Antibody Therapy of CLL

1.4.1 Rituximab Therapy of CLL

Immunotherapy with unconjugated monoclonal antibodies represents a new mode of therapy for CLL. Of the many antibodies tested in CLL, rituximab and Campath-1H have the highest reported success rates to date (37-49). In contrast, rituximab is directed at a B-cell specific antigen and therefore is associated with much less immunosuppression. While initial studies of the chimeric anti-CD20 antibody rituximab demonstrated disappointing results in small-cell lymphocytic lymphoma (SLL) and CLL (41-43), subsequent studies directed at overcoming the adverse pharmacokinetic parameters have led to improving efficacy in this disease (40). Down-regulation of mcl-1 and XIAP occurred in most patients irrespective of response (49). As pre-treatment mcl-1 levels have been associated with lack of complete response to treatment in CLL, this may represent the mechanism by which rituximab chemosensitizes tumor cells to chemotherapy. Given the lack of overlapping toxicity between standard therapy (e.g. alkylator and purine analog-based therapy), combination approaches with rituximab appear warranted.

1.4.2 CAMPATH-1H Therapy with CLL

CAMPATH-1H is a humanized antilymphocyte monoclonal antibody (MAB) engineered by grafting the rodent hypervariable complementarity determining regions (CDR) into a human immunoglobulin variable framework region (51). It is one of a series of MABs directed against the CD52 surface antigen, expressed on lymphocytes at nearly all stages of differentiation.

The Campath-1 antigen (designated CD52 by the Fourth International Workshop on Human Leukocyte Differentiation Antigens in 1989) is a heavily glycosylated, non-modulating glycoprotein of molecular weight 21-28kD which in humans is predominantly expressed on peripheral blood lymphocytes, monocytes, and macrophages. It is estimated that peripheral blood lymphocytes have approximately $5x10^5$ antibody binding sites per cell (52). Antibodies raised against this antigen efficiently lyse lymphocytes in the presence of human complement. However, they do not appear to lyse monocytes (53).

1.4.2.1 In the three Phase I trials (001,002,003) by Burroughs Wellcome (BW), CAMPATH-1H showed evidence of activity in patients with CLL, especially in reducing the number of circulating leukemia cells, splenomegaly and bone marrow infiltration. Many patients entering these trials had previously received treatment with alkylators and/or fludarabine. In two Phase II studies (005 and 009), CAMPATH-1H produced a response rate (based on intent to treat analysis) of 33% in 76 patients, including 42 who were previously treated with fludarabine (91-95).

Of the 16 major responses (50% or greater reduction in disease), 8 occurred in patients with CLL or prolymphocytic leukemia (PLL). Forms of non-Hodgkins lymphoma (NHL) in which responses were observed included small lymphocytic lymphoma (2 cases), lymphoplasmacytoid follicular (1 case), small cleaved cell (1 case), diffuse small cleaved cell (2 cases), diffuse mixed cell (1 case), and mycosis fungoides (2 cases).

The majority of patients experienced at least 50% reduction of high lymphocyte count. Clearance of bone marrow infiltration and reduction in splenomegaly was also achieved in a number of patients. CAMPATH-1H had less effect in reducing lymphadenopathy, particularly bulky areas, possibly due to poor access of the antibody to sites of bulky disease and inadequate effector mechanisms at such locations.

Rawston et al reported on 10 patients with CLL who were refractory to conventional therapy, including fludarabine, who were treated with CAMPATH-1H (54). The regimen was 30 mg given three times a week for 6 weeks. Patients were treated with co-trimoxazole and fluconazole prophylactically. Six of the 10 patients have received a full

course. Most patients experienced some minor infusion-related symptoms, such as rigors, during therapy. While Campath-1H is active in the treatment of CLL, the immunosuppression produced by this agent can be profound (47-49).

Osterborg et al have published efficacy and safety results for previously treated CLL patients (45). Twenty-nine patients who had relapsed after an initial response (n=8) or were refractory (n=21) to chemotherapy were treated with CAMPATH-1H 30 mg administered as a 2-hour IV infusion three times weekly for a maximum of 12 weeks. Of them, 8 had been previously treated with chlorambucil and prednisone only, 3 with prior fludarabine, 14 with CHOP or similar regimens, and 7 with various single-agents. There was 1 CR and 11 PRs, for an overall 42% (95% CI: 23%-61%) response rate. Three of the 8 patients (38%) with a relapse and 9 of 21 refractory patients (43%) responded to CAMPATH-1H therapy. CLL cells were rapidly eliminated from the blood in 28 of 29 patients (97%). CR in the bone marrow was obtained in 36% and splenomegaly resolved completely in 32%. Lymphadenopathy was normalized in only 2 patients (7%).

1.4.2.2 Bowen et al reported on the subcutaneous administration of CAMPATH-1H in fludarabine-resistant/relapsed CLL and B-PLL (46). Seven patients with B-cell leukemia (6 with CLL and 1 with B-PLL) were treated with CAMPATH-1H subcutaneously (SC) three times a week for 6-12 weeks. The initial dose was 10 mg with further injections of 30 mg given on an outpatient basis. Previously, four of the patients were resistant to fludarabine and three had a PR before relapsing. The patient with B-PLL achieved a CR and three of the CLL patients achieved a PR (two of these patients were retreated). The three remaining patients were non-responders. Three patients were transfusion dependent before CAMPATH-1H, and all three became transfusion independent after treatment. Cytomegalovirus (CMV) reactivation occurred in 3/7(43%).

1.4.2.3 Lundin et al. recently updated the experience of the Karolinska group utilizing subcutaneous administration of CAMPATH-1H for previously untreated patients with CLL (55). CAMPATH-1H was administrated three times a week (TIW) subcutaneously for 12-18 weeks to forty-one patients the majority of whom had advanced disease. The initial dose was 3 mg, but was escalated rapidly to 30 mg/ml/TIW. The medication was self-administered at home after week 2. Acyclovir, fluconazole, co-trimoxazole, and allopurinol were given concomitantly. Responses were seen in 81% of the patients (17% CR, 64% PR). Although overall response by disease sites was satisfactory

(79-97%), the medication was most successful in blood and least successful in lymph nodes. The maximum response in blood was rapid, those in nodal, splenic, and marrow less rapid. Most side effects occurred as "first dose reactions". Non-hematologic side effects, apart from fever, were significantly reduced by SQ administration versus IV administration. Systemic reactions included rigors (17%), fever (68%), and fatigue (3 patients – grade II-III). No episodes of rash/urticaria, bronchospasm, hypotension, or nausea were observed. Local skin reactions (88% of patients) were grade 0-II and generally disappeared during continued CAMPATH-1H treatment. These consisted of erythema/edema, pruritis, and slight pain. However, three patients were withdrawn from the study because of severe local reactions (pain) or systemic symptoms (fever, fatigue). Hematologic toxicity was still significant with 21% of patients developing transient grade IV neutropenia. Five patients (13%) developed two or more episodes of grade IV neutropenia successfully treated with a "few" injections of G-CSF. No patients developed febrile neutropenia. CMV reactivation occurred in 4/41(10%).

1.4.2.4 Albitar et al, while studying the pharmacokinetics of CAMPATH-1H, in the setting of minimal residual disease (MRD), suggested that CLL patients with higher levels of residual disease may require higher doses of CAMPATH-1H to eradicate disease and that detectable plasma levels of CAMPATH-1H may be necessary for achieving CR (98). The dose of CAMPATH-1H on the present study is considerably higher and, hopefully, will overcome resistance to eradication of MRD.

1.5 Combination of Chemotherapy and Immunotherapy of CLL

1.5.1 CALGB performed a randomized phase II trial of sequential versus concurrent rituximab (50). All patients fulfilled the NCI definition of B-CLL and requirement for therapy. Patients on the sequential arm (fludarabine then rituximab) received fludarabine (25 mg/m^2 dl-d5 repeated monthly x6) induction followed by rituximab (375 mg/m^2 repeated weekly x4). Patients on the concurrent arm (fludarabine and rituximab) received therapy identical to the sequential arm except rituximab (375 mg/m^2) was also administered (day 1 and 4 of cycle 1; day 1 of cycles 2 of 6) with fludarabine induction therapy. A total of 104 patients have been enrolled. Fludarabine plus rituximab induction toxicity included neutropenia (grade 3 or 4, 77%), thrombocytopenia (grade 3 or 4, 20%) and infection (grade 3 or 4, 18%). Fludarabine induction toxicity included neutropenia (grade 3 or 4, 41%), thrombocytopenia (grade 3 or 4, 12%), and infection (grade 3, 21%). There was no increase in the frequency of opportunistic infections noted in the concurrent (15%) versus the sequential arm (26%). Overall consolidation was tolerated well in both arms. Response data using the NCI criteria are:

Treatment	No. Patients	No. CR (%)	No. PR (%)	No. OR(%)
Fludarabine plus R	51	24 (47)	22(43)	46 (90)
Fludarabine then R	53	15 (28)	26 (69)	41 (77)

Key: R= Rituximab, CR=complete response, PR=partial response, OR overall response

The FCR combination (fludarabine 25 mg/m^2/d x3), cyclophosphamide 250 mg/m^2/d x3, rituximab 375 mg/m^2/day 1) was recently reported to induce 67% CR, 19%nPR, and 18% PR in 135 CLL patients when used as initial therapy. RT-PCR testing for MRD was performed on bone marrow at the end of therapy (usually 6 cycles) using CD5+ 19+ coexpression. None of the MRD negative patients by RT-PCR have had a clinical or flow relapse (57).

1.5.2 We have recently begun a study of pentostatin, cyclophosphamide and rituximab (PCR) as a collaborative effort with the James Cancer Center (Ohio State) for patients with untreated B-cell chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma. Toxicity has been modest. Weiss et al (personal communication) have treated approximately 23 previously treated patients (MSKCC; Cleveland Clinic). A full analysis of response and toxicity has not been published. However, one patient suffered grade 5 pulmonary toxicity (MSKCC) and several patients were removed from study at the Cleveland Clinic. No further details are available. Data on the use of pentostatin and rituximab have been published in abstract form. There were 19/60 patients (low grade (NHL)) with the diagnosis of small lymphocytic lymphoma. Specific responses in this group were not published. However, there was a 70% overall response percentage. There were two deaths on study (COPD, TTP). Toxicities

included neutropenia (6%), fever, shingles, headache (3.3%), anemia, atrial fibrillation, bronchospasm, chills, dehydration, febrile neutropenia, hypotension, mucositis, pneumonia, increased SGOT, and vertigo (1.7%)(93).

Rev. 7/07

Rev. 7/07

1.6 Rationale For Current Clinical Study

We wish to combine an effective combination chemotherapy regimen that is associated with a high complete response rate with immunotherapy (Rituximab and CAMPATH-1H) for chemosensitization and eradication of minimal residual disease (MRD). Multiparameter immunophenotypic analysis detecting aberrant phenotypes has been successful as a probe to detect MRD and will be used as part of this study (see Section 2.0)(96). These results appear similar to quantitative molecular monitoring utilizing allele-specific oligonucleotide PCR (ASO-PCR) (97). The combination of fludarabine and rituximab has demonstrated promising results, but a high rate of grade 3 and 4 neutropenia (56). Similarly, addition of rituximab to the fludarabine/cyclophosphamide combination piloted by MD Anderson has resulted in high responses but required lowering the chemotherapy doses (57,58). CAMPATH-1H in combination with fludarabine has shown significant activity in refractory CLL (59). Rituximab has been combined with pentostatin in a Phase 2 study (61). The results have been published in abstract form (61,93). Of 54 evaluable patients, 18 (33.3%) achieved an objective response 5.5% CR, 3.7% CRn, 16.7% PR, 7.4% nPR. Response rates were similar in previously treated and untreated patients (33.4% and 33.3% respectively). Grade ≥ 3 toxicities occurred in 27 patients (neutropenia (29%), febrile neutropenia (1.6%), leukopenia (8.1%), thrombocytopenia (5.3%), pulmonary (3.2%), gastrointestinal (3.2%), and infection (3.2%)). One death was reported as “treatment-related pneumonia”. The preliminary results of the combination of pentostatin, cyclophosphamide, and rituximab in previously treated patients have been communicated to us (Weiss, personal communication), but have not been officially analyzed. Toxicity is described in Section 1.5.2. A study of previously untreated CLL patients utilizing PCR is being undertaken at Mayo Clinic. Preliminary toxicity results are outlined in Section 1.5.2. The addition of rituximab, an agent that favorably down-modulates mcl-1 and XIAP in CLL B cells, may chemosensitize these cells to the effects of pentostatin and cyclophosphamide. Recently both rituximab and CAMPATH-1H have been combined demonstrating significant activity (61,62). As discussed in Sections 1.4.2.2 and 1.4.2.3, the SC administration of CAMPATH-1H would appear to have a better therapeutic index with less side effects. Therefore, its incorporation in this study would likely result in less adverse events than might be expected with IV administration. For those patients who achieve a partial response or progress on therapy, a conventional course of CAMPATH-1H (18 weeks) may offer a reasonable option for response and clinical benefit, as there are few treatment alternatives in the setting of third line options. In conjunction with this unique combination therapy, we hope to examine a variety of relevant correlative endpoints (detailed in the following sections) that will allow us to distinguish features of leukemic cell biology that relate to resistance and patient outcome to the chemoimmunotherapy of our clinical protocol.

1.7 Rationale for Ancillary Studies

We intend to study critical biologic events in the CLL cells of patients entered onto this protocol. Cytogenetic analysis of CLL cells has been undertaken by numerous investigators and has been related to stage of disease, overall prognosis, and sensitivity to therapy (65-67, 75-81).

We will also determine the Ig variable region sequence of the CLL B cells in order to determine if they are either germline or somatic mutation type clones. This is relevant since recent data (63-66) demonstrates CLL patients with germline type clones have a worse clinical outcome compared to somatic mutation type clones. In addition to the apparent predictive value of Ig V heavy chain region sequence to clinical outcome, the germline clones had genetic defects that were dissimilar from the somatic type clones. A retrospective analysis on frozen CLL cells for patients entered on 3 North Central Cancer Treatment Group (NCCTG) clinical trials has shown a trend towards longer time to progression for CLL patients with somatic type clones compared to germline type clones (66). We will examine the presence of germline or somatic type clones and evaluate this combination of genetic data to clinical outcomes on this trial. Genetic analysis for determination of therapeutic efficacy of monoclonal antibodies (67,69) will be incorporated in these studies. The techniques for Ig V heavy chain region sequencing have been established at the Mayo Clinic (66).

We have recently determined that abnormal angiogenesis exists in B-CLL (68). Increased marrow blood vessels appear to be positively associated with increasing stage of disease. The mechanism for this abnormal angiogenesis is unclear but preliminary work by us has shown that CLL cells produce both pro- and anti-angiogenic factors. The balance of these two types of vascular growth factors are likely to be critical to the induction of tumor related angiogenesis. However we have also shown that CLL B cells express mRNA for VEGFR1 and VEGFR2 (vascular endothilial growth factor receptor) thus raising the possibility of an autocrine pathway for VEGF (vascular endothilial growth factor receptor) that could impact on CLL B cells. The levels of pro and anti-angiogenic factors in CLL patients progressing through this clinical protocol will be studied. The change in both the levels and ratios of angiogenesis factors will be compared to their clinical responses.

Since CLL patients have deficient T cell repertoire with the expanded CLL B cell clone it is important to know if this immunodeficiency parameter can be restored with therapy. We are particularly interested in knowing if the extent of T cell repertoire deficiency and changes induced by treatment can be associated with clinical responses and/or toxicities of the treated CLL patients. Therefore we intend to study the T cell repertoire by flow cytometry at patient entry to the study and then at various times after completion of the chemoimmunotherapy protocol.

Recent studies have been able to identify patients who are poorly responsive to CAMPATH-1H (69) and these studies will be incorporated into the protocol. Theoretically, relapse of CLL after treatment evolves from the proliferation of “minimal residual disease (MRD)” progenitors. Techniques established for the detection of MRD (70-74) will be incorporated into these studies. These will include flow cytometric and real-time PCR assays.

1.8 Gender and Ethnicity Statement

1.8.1 Entry to this study is open to both men and women, and to persons of any national or ethnic group. ECOG's previous CLL studies enrolled approximately 70% men, 30% women, 82% white, 12% black, and 6% other ethnic backgrounds. We anticipate that entry of women and minorities to this study will show similar proportions. We are aware of no literature citing differential treatment effects by gender or ethnicity in relapse and refractory CLL and therefore have not incorporated separate accrual targets for such patient groups.

2. Objectives

2.1 Clinical Objectives

2.1.1 Primary Objectives

2.1.1.1 To evaluate the objective (complete remission = CR, nodular partial remission = nPR, partial remission = PR) response rate of pentostatin, cyclophosphamide, and rituximab (PCR) in patients with previously treated B-cell chronic lymphocytic leukemia (CLL).

2.1.1.2 To assess the presence of minimal residual disease (MRD) at the completion of the PCR regimen and after Campath-1H in patients who achieve a CR or nPR.

2.1.2 Secondary Objectives

2.1.2.1 To evaluate the toxicity of the combined therapy, PCR with CAMPATH-1H, in patients with previously treated B-CLL.

2.1.2.2 To evaluate the overall survival and progression-free survival of patients treated with pentostatin, cyclophosphamide, and rituximab with CAMPATH-1H (PCR → CAMPATH-1H).

2.1.2.3 To evaluate the number of patients who after PCR (or during PCR for PD), only achieve a PR, SD, or PD and who subsequently convert to a higher response category after Campath-1H.

2.2 Laboratory Objectives

2.2.1 To assess the angiogenic profile (i.e. secretion levels of pro versus anti-angiogenic molecules) (100) of CLL B cell clones as well as bone marrow angiogenesis (i.e. vascular density by immunohistochemistry) (68) at baseline, after PCR, after Campath-1H, every six months (serum only), and at time of response assessment (marrow).

2.2.2 To determine the V_H gene mutation status and CD38 expression of the B-CLL clones at study entry and at the end of the therapy and assess the association between the VH gene mutation status and CD38 expression and clinical outcome.

2.2.3 To acquire surface phenotype (by flow cytometry) and genetic defects (by CLL FISH panel) (99) information on CLL-B cell clones. This latter information will be studied for association with clinical outcome.

2.2.4 The T cell status will also be monitored by repertoire and flow cytometry analysis to determine the nature and extent of T cell deficiency induced by the PCR and Campath treatment in our patient cohort. This latter information will be studied for association with clinical outcome and toxicities of the CLL cohort.

3. Selection of Patients

Rev. 8/05

Each of the criteria in the following checklist must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Rev. 8/05

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the ECOG-ACRIN Operations Office - Boston at (617) 632-3610.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

_____ 3.1 Step 1: Induction Eligibility Requirements

3.1.1 Patients must have a diagnosis of B-CLL, as defined by the NCI criteria below (2). All three criteria must be met:

Rev. 6/05

3.1.1.1 Patients must have a peripheral blood absolute lymphocyte count of > 5,000/mm^3 obtained within 2 weeks prior to registration.

Count: _____ Date of Test: _____

3.1.1.2 The lymphocytosis must consist of small to moderate size lymphocytes, with ≤ 55% prolymphocytes, atypical lymphocytes, or lymphoblasts morphologically.

3.1.1.3 Patients must have phenotypically characterized B-CLL defined as: 1) the predominant population of cells share B-cell antigens with CD-5 in the absence of other pan-T-cell markers (CD-3, CD-2, etc.); 2) B-cell expresses either κ and λ light chains; and 3) surface immunoglobulin (slg) with low-cell surface density expression.

NOTE: Splenomegaly, hepatomegaly, or lymphadenopathy are not required for the diagnosis of CLL. However, if palpable adenopathy is present, bidimensional measurements are required pretreatment and at scheduled disease assessments in order to determine response. (Provide measurements on a minimum of 2 of the largest nodes but no more than 5.)

Rev. 7/07

Rev. 6/05

_____3.1.2 Patients must require chemotherapy. The last administration of chemotherapy must have been completed ≥ 6 weeks prior to study treatment. Any of the indications below for chemotherapy must be met:

Rev. 6/05

Rev. 7/07

3.1.2.1 One or more of the following disease-related symptoms:

a. Weight loss ≥ 10% within the previous 6 months (grade 2 or higher)
b. Extreme fatigue (grade 3 or higher)
c. Fevers > 100.5ºF for 2 weeks without evidence of infection (grade 1 or higher)
d. Night sweats without evidence of infection (drenching)

3.1.2.2 Evidence of progressive marrow failure as manifested by the development of or worsening anemia (≤ 10 g/dl) and/or thrombocytopenia (≤ 100,000/mm^3).

3.1.2.3 Massive (i.e. > 6 cm below left costal margin) or progressive splenomegaly.

3.1.2.4 Massive nodes or clusters (i.e. > 10 cm in longest diameter) or progressive adenopathy.

3.1.2.5 Progressive lymphocytosis with an increase of > 50% over 2 month period, or an anticipated doubling time of less than 6 months.

_____ 3.1.3 Patients must have either: (1) demonstrated progression after at least one cycle of either an alkylating agent-based or purine nucleoside based (i.e. fludarabine) regimen, (2) failed to achieve a meaningful response, or (3) relapsed after prior therapy. Patients who have relapsed with a pentostatin-based regimen may be eligible if the response was greater than 12 months.

Rev. 7/07

_____ 3.1.4 Patients may have received prior Rituximab therapy but at least eight weeks should have elapsed between the last Rituximab dose and registration.

_____ 3.1.5 Patients must not have had previous CAMPATH-1H therapy prior to entering the study. Patients may have had previous PCR therapy or components thereof, however, they must have completed pentostatin and cyclophosphamide ≥ 1 year from date of registration.

Rev. 5/06
Rev. 7/07

_____ 3.1.6 Serum creatinine must not be greater than 2 mg/dl obtained ≤ 2 weeks prior to registration. If serum creatinine is greater than 1.5 mg/dl but less than 2mg/dl, the creatinine clearance calculated from a 24 hour urine collection must be ≥ 30 ml/min.

NOTE: May be calculated using the Cockcroft-Gault Equation: (140-age)*wt(kg)/([Cr]*72). For women, the calculation may be multiplied by 0.85.

Rev. 1/09

Serum creatinine: _____ Date of Test: _____

_____ 3.1.7 Bilirubin must be ≤ 2 mg/dl, unless secondary to tumor or hemolysis, obtained ≤ 2 weeks prior to registration.

Bilirubin: _____ Date of Test: _____

NOTE: Patients with Gilbert's syndrome will be eligible for study.

_____ 3.1.8 Patients with active infections requiring oral or intravenous antibiotics are not eligible for entry onto the study until resolution of the infection and completion of antibiotics.

_____ 3.1.9 Age ≥ 18 years.

_____ 3.1.10 Women must not be pregnant or breast feeding because it is unknown what effect these drugs will have on a fetus or child.

All females of childbearing potential must have a blood test or urine study ≤ 2 weeks prior to registration to rule out pregnancy.

Woman of childbearing potential? _____ (Yes or No)

Date of Test: _____

_____ 3.1.11 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception.

_____ 3.1.12 Patients must have ECOG performance status of 0-2.

_____ 3.1.13 Patients with a second malignancy other than squamous/basal cell carcinoma of the skin or *in situ* carcinoma of the cervix are not eligible unless the tumor was curatively treated at least two years previously.

_____ 3.1.14 Patients with grade III or IV heart failure according to the New York Heart Association functional classification are not eligible.

_____ 3.1.15 Patients whose marrow function is attributable to dysplasia related to prior therapy are not eligible.

_____ 3.1.16 Patients must be tested for hepatitis B virus infection. Those who are carriers of the virus or who test positive for the virus will be allowed to enter the study, but will be closely monitored for clinical and laboratory signs of active HBV infection and hepatitis (see Section 7).

Result of test: _____ Date of Test: _____

3.2 Step 2 : Eligibility Requirements For Re-registration to CAMPATH-1H

Rev. 7/07

NOTE: Response to Step 1 must be determined before registration to Step 2.

To be registered to Arm B, patients must

- meet all criteria for clinical CR response
- have first post-treatment BM BX at 8 weeks after all criteria are first met for clinical CR
- start treatment approximately 12 weeks after last dose (6th cycle) of PCR on Step 1
- be free of symptoms as specified in 3.1.2.1

To be registered to Arm C, patients must

- meet all criteria for PR, SD or PD
- have completed 6 cycles of PCR, unless determined to have progressive disease on PCR treatment
- if determined to have progressive disease, stop treatment with PCR and begin treatment for Arm C CAMPATH-1H 30 mg SQ TIW for 18 weeks, beginning CAMPATH-1H no sooner than 2 weeks and no later than 8 weeks after the last dose of PCR

_____ 3.2.1 Patients must have an ECOG performance status of 0-2.

_____ 3.2.2 Serum creatinine must not be greater than 2.0 mg/dl obtained ≤ 2 weeks prior to re-registration. If serum creatinine is greater than 1.5 mg/dl, the creatinine clearance calculated from a 24 hour urine collection must be ≥ 40 ml/min.

Serum creatinine: _____ Date of Test: _____

Creatinine clearance (if required): _____

_____ 3.2.3 Bilirubin must be ≤ 2 mg/dl, unless secondary to tumor or hemolysis, obtained ≤ 2 weeks prior to re-registration.

Bilirubin: _____ Date of Test: _____

NOTE: Patients with Gilbert's syndrome will be eligible for study.

_____ 3.2.4 Patients with active infections requiring oral or intravenous antibiotics are not eligible for entry onto step 2 until resolution of the infection and completion of antibiotics.

4. Registration Procedures

Submitting Regulatory Documents

Before an ECOG-ACRIN Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
   Or
   B. HHS 310 Form.
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed at http//www.ctsu.org/rss2_page.asp**. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail** CTSUContact@westat.com**.**

Rev. 1/14

Patients must not start protocol treatment prior to registration.

Treatment should start within three working days after registration

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (https://webreg.ecog.org). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG-ACRIN Operations Office

- Boston at (617) 632-2022, Monday through Friday 9:00am-5:00 pm Eastern Time. Please note that a password is required to use this program. The following information will be requested:

4.1 Step 1: Induction (Arm A)

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution name and/or affiliate

4.1.2.2 Investigator's name

4.1.3 Patient Identification

4.1.3.1 Patient's initials and chart number

4.1.3.2 Patient's Social Security number

4.1.3.3 Patient Demographics

4.1.3.3.1 Sex

4.1.3.3.2 Birthdate (MM/YYYY)

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.4 Nine-digit zip code

4.1.3.5 Method of payment

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.1.5 Additional Requirements

4.1.5.1 Patient must provide signed and dated written informed consent.

4.1.5.2 Correlative study samples should be submitted as outlined in Section 11.0.

Rev. 6/05

NOTE: Institutions outside of the United States and Canada are not required to submit fresh samples because of the costs and problems associated with international shipping.

Rev. 6/05, 5/06

[Section 4.1.5.3 deleted in Addendum #9, 5/06]

4.1.6 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

Rev. 8/05

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the E2903 Forms Packet. Document the reason for not starting protocol treatment on one of the baseline forms.

4.2 Step 2: Re-registration Procedures to Campath-1H (Arm B and Arm C)

Rev. 7/07

If patient achieves confirmed CR or nPR upon re-evaluation, patient will be registered to receive CAMPATH-1H for four weeks (Arm B). If patient achieves

Rev. 7/07

PR, stable disease or PD upon re-evaluation, patient will be registered to receive CAMPATH-1H for eighteen weeks (Arm C).

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution name and/or affiliate

4.2.2.2 Investigator's name

4.2.3 Patient Identification

4.2.3.1 Patient's initials and chart number

4.2.3.2 Patient's Social Security number

4.2.3.3 Patient Demographics

4.2.3.3.1 Sex

4.2.3.3.2 Birth date (MM/YYYY)

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit zip code

4.2.3.4 Method of payment

4.2.4 Eligibility Verification

Rev. 7/07

Patients must meet all of the eligibility requirements listed in Section 3.2. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.2.5 Additional Requirements

Rev. 1/09

4.2.5.1 Correlative study samples should be submitted as outlined in Section 11.0.

Rev. 6/05

NOTE: Institutions outside of the United States and Canada are not required to submit fresh samples because of the costs and problems associated with international shipping.

Rev. 6/05, 5/06

[Section 4.2.5.2 deleted in Addendum #9, 5/06]

4.2.6 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted

Rev. 8/05

according to the E2903 Forms Packet. Document the reason for not starting protocol treatment on one of the baseline forms.

5. Treatment Plan

NOTE: For G-CSF administration, either Neupogen® or Neulasta® may be used.

NOTE: Doses based on actual body weight.

5.1 Step 1 (Arm A): Rituximab, pentostatin, and cyclophosphamide

5.1.1 Pre-medication

During the first week of therapy, Tylenol 650 mg PO and diphenhydramine (Benadryl) 50 mg IV should be administered 30 minutes prior to rituximab to prevent infusion-related toxicity.

Allopurinol will be required on days 0-14 of cycle 1. Allopurinol will be given at 300 mg/day PO x 15 days.

Antiemetic medications such as Kytril 2 mg PO should be given 1 hour to thirty minutes prior to chemotherapy and 12 hours after chemotherapy if necessary. Additional prophylactic antiemetic therapy will be left to the discretion of the treating physician. Steroids are discouraged.

Patients should be encouraged to drink fluids the night before treatment and will receive approximately 1-liter IV hydration over 1 hour prior to chemotherapy – hydration on days with rituximab but without chemotherapy is left to the discretion of the investigator.

5.1.2 Rituximab, Pentostatin, and Cyclophosphamide

Rev. 5/06

Treatment will consist of 6 cycles of pentostatin, cyclophosphamide, and rituximab (PCR) given every 28 days. See Table 5.1.2a and Sections 5.1.2.1 and 5.1.2.2 for dosing instructions.

Patients will be assessed with physical examination, assessment of liver/spleen and measurement of lymphadenopathy, CBC, and chemistries prior to each cycle. Patients meeting criteria for prohibitive toxicity or progressive disease will not receive further PCR treatment on study. However, patients demonstrating progressive disease, stable disease or partial response will then be given CAMPATH-1H as per protocol (see Section 6.0).

Table 5.1.2.a: PCR (Pentostatin, Cyclophosphamide, Rituximab) Dose Schedule

	Agent	Dose	Route	Cycles	Rx day(s)	Frequency
Rev 3/05	Rituximab**	Day 1 of therapy 100 mg IV over 4 hours (25 mg/hr) Day 3 of therapy 375 mg/m^2 IV at 50 mg/hr (if no prior reaction on day 1). Increase rate by 50mg/hr every 30 minutes, if no reaction, to a maximum of 400 mg/hr. Day 5 of therapy 375 mg/m^2 IV at 100 mg/hr for the first 30 minutes. Increase rate by 100mg/hr every 30 minutes, if no reaction, to a maximum of 400 mg/hr.	IV in 250-500 mL NS	1	1, 3, 5	This schedule for the first week only
Rev. 5/06	Rituximab**	375 mg/m^2 will be repeated as a single IV infusion Day 1 of Week 5, 9, 13, 17 and 21.	IV	2-6	1	Q 4 weeks
Rev. 5/06, 1/09	Pentostatin**	4 mg/m^2 on Day 1 of each cycle	IV over 10-30 minutes in 250 mL NS or D5W	1-6	1	Q 4 weeks
Rev. 5/06, 1/09	CTX**	600 mg/m^2 on Day 1 of each cycle	IV over 30-60 minutes in 250-500 mL NS	1-6	1	Q 4 weeks

**** The order of drug treatment is as follows in this sequence of administration: (1) Rituximab, (2) Pentostatin, (3) cyclophosphamide.**

Rev. 12/05

Table 5.1.2b G-CSF* Dose Schedule

Agent	Dose	Route	Cycles	Rx day(s)	Frequency
G-CSF*	5 mcg/kg	SQ	All	3-12 (see Section 5.1.4.4)	Each Treatment Cycle

Rev. 1/09

Rev. 5/06, 1/09

* Neulasta, at a dose of 6 mg SQ on day 1 post chemo, Q 4 weeks, may be substituted for G-CSF at physician's discretion. See Section 5.1.4.4.

NOTE: Patients may have their infusions via the following methods: Port-a-cath, central line, PIC, peripheral line, or Hickman.

5.1.2.1 Rituximab will be administered as follows:

During the first week of therapy, Tylenol 650 mg PO and diphenhydramine (Benadryl) 50 mg IV should be administered 30 minutes prior to rituximab to prevent infusion-related toxicity.

Shortness of breath, rigors, and other infusion-related toxicity has been noted more frequently during the first several treatments. Rarely, pulmonary failure with infiltrates and edema resulting in fatalities has been observed. Vital signs are recommended to be measured

Rev. 1/14

every 15 minutes for the first 2 hours with the first dose of rituximab, with each dose escalation and then as clinically indicated. Temperature should be taken prior to each treatment and repeated as clinically indicated throughout each infusion. The treatment area should be sufficiently prepared to allow easy access to supportive care medications and measures, such as Demerol for IV push, O_2 supplementation and nebulized albuterol, warm blankets, IV fluid for bolus, and access to crash cart (84.85).

5.1.2.1.1 For the first infusion:

All patients will receive diphenhydramine 50 mg IV and Tylenol 650 mg po 30 minutes prior to initiation of rituximab.

All patients will receive a 100 mg dose (regardless of weight/BSA) of rituximab. The infusion rate will be 25 mg/hr throughout day 1 treatment (the rate will NOT be escalated on this day).

If rigors occur, rituximab administration should cease temporarily and meperidine 25 mg IVP and promethazine 12.5 mg IVP should be administered.

If transient bronchospasm occurs, rituximab administration should be interrupted. If these symptoms persist, consideration should be given to administering hydrocortisone 100 mg and an albuterol (or other B_2 agonist) inhaler. Once this has returned to grade 1 in severity, rituximab administration can resume.

5.1.2.1.2 For the second and subsequent infusions:

All patients will receive diphenhydramine 50 mg IV and Tylenol 650 mg PO 30 minutes prior to initiation of rituximab.

Rev. 3/05

All patients will receive rituximab 375 mg/m^2. For the second administration of cycle 1 (Day 3) the rituximab will be administered at an initial rate of 50 mg/hr and increased by 50 mg/hr every 30 minutes, if there are no reactions, to a maximum of 400 mg/hr. For the third administration of cycle 1 (Day 5) and for all subsequent administrations (cycles 2-6) the rituximab infusion will begin at 100 mg/hr with 100 mg/hr increments every 30

minutes, if there are no reactions, to a maximum of 400 mg/hr.

If rigors occur, rituximab administration should cease temporarily and meperidine 25 mg IV and promethazine 12.5 mg IV should be administered.

If transient bronchospasm occurs, rituximab administration should be interrupted. If this persists, consideration to administering hydrocortisone 100 mg and an albuterol (or other B_2 agonist) inhaler should be given. Once this has returned to grade 1 in severity, rituximab administration can resume.

5.1.2.1.3 **In patients with high leukocyte counts**, close observation for potential toxicities should occur (84,85). If marked reduction in circulating lymphocytes is noted, close attention to the possibility of **acute tumor lysis** should occur. As treatment with rituximab may result in acute but temporary reduction in platelets, patients with baseline platelet counts ≤ 20,000/μL should receive platelet transfusion prior to rituximab therapy. Patients should be encouraged to drink abundant fluid prior to the first treatment. Additional measures for hydration should be considered in patients with bulky adenopathy or leukocytes > 50,000/μL. Physicians are encouraged to contact the Study Chair with any questions regarding these supportive care issues.

5.1.2.2 Pentostatin and cyclophosphamide will be administered as follows:

Pentostatin to be given at 4 mg/m^2 either as an IV push or IV over 10-30 minutes in 250 mL NS or D5W on day 1 every 4 weeks of cycles 1-6.

Rev. 12/05, 7/07

Cyclophosphamide to be given at 600 mg/m^2 IV over 30-60 minutes in 250 mL NS on day 1 every 4 weeks of cycle 1-6.

Rev. 7/07

5.1.3 Dose Modification Based on Toxicity:

Rev. 5/11

All toxicities should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The CTCAE version 4.0 is identified and located on the CTEP website at http://ctep.cancer.gov. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

If multiple toxicities are seen, administer dose based on greatest reduction required for any single toxicity observed. Reductions apply to treatment given in the preceding cycle and are based on toxicities observed since the prior dose.

5.1.3.1 Dose Modifications for Rituximab

No dose modifications for Rituximab. If grade 4/5 toxicity occurs (see CTCAE v4.0), please contact the principal investigator for further guidelines.

Dose modifications for Pentostatin and Cyclophosphamide (CTX)

TOXICITY	AGENT	DOSAGE CHANGE
Pentostatin or CTX		
At time of retreatment cycles 2-6		
ANC ≥ 1,000, or PLT ≥ 50,000	Pentostatin and Cyclophosphamide	Rx @ 100% doses for Pentostatin and CTX.
ANC ≤ 1,000, or PLT ≤ 50,000	Pentostatin and Cyclophosphamide	Delay Rx 1 week. If counts > these levels, resume Rx @ 100% dose level.
After 1 week delay		
ANC 500 – 1,000 or PLT 30,000-50,000	Pentostatin and Cyclophosphamide	↓ pentostatin to 1 mg/m^2 and resume. ↓ CTX to 300 mg/m^2 and resume.
ANC ≤ 500 or PLT ≤ 30,000	Pentostatin and Cyclophosphamide	Discontinue Rx and go to event monitoring.
Non-hematologic: Grade 3 organ toxicity (except fever, hyperglycemia, GI, infection) Grade 4 GI		Discontinue treatment and go to event monitoring.
There are no pentostatin or cyclophosphamide modifications for interval toxicity		

Rev. 5/06

5.1.3.1.1 Serum creatinine will be determined within 14 days of PCR treatment. Serum creatinine must not be > 2mg/dl. (If it is > 2mg/dl, cycle should be delayed until creatinine level returns to ≤ 2 mg/dl. If creatinine level remains above 2 mg/dl for longer than 2 weeks, the patient will come off study treatment with the choice of subsequent treatment to be decided by the treating physician). If the creatinine level is > 1.5 mg/dl, but ≤ 2mg/dl, a creatinine clearance will be obtained. No dose reduction will be made for a creatinine clearance ≥ 60 ml/min. For a creatinine < 60 ml/min, a dose reduction of 50% in the pentostatin dose will be made.

Rev. 1/09

NOTE: May be calculated using the Cockcroft-Gault Equation: (140-age)*wt(kg)/([Cr]*72). For women, the calculation may be multiplied by 0.85.

There are no safe guidelines for administration of pentostatin in patients with a creatinine clearance of < 30 ml/min. This will be the minimum clearance for patients on this study and so any patients whose clearance is < 30 ml/min will discontinue protocol therapy.

Rev. 12/05, 5/06

5.1.3.2 Patients who suffer grade 4 toxicity unrelated to the leukemia, using the CTCAE, will be removed from study. This may occur either during the PCR phase or during Campath-1H consolidation (or treatment for PR, PD and SD patients). This includes allergic manifestations, blood and bone marrow suppression unrelated to the leukemia, and cardiovascular, dermatologic, renal, gastrointestinal and neurologic events. For grade 4 infection/febrile neutropenia, removal from study will be left to the discretion of the investigator. If a patient develops grade 2 or greater thrombocytopenia during CAMPATH-1H administration, the medication will be withheld until this resolves. Both myelosuppression and immune-mediated mechanisms have been implicated. Myelosuppression and drug-induced immune thrombocytopenia should resolve once the CAMPATH-1H is stopped (up to four weeks for recovery). If immune-mediated thrombocytopenia (ITP) occurs, more aggressive measures are to be taken (as have been reported) and these are left to the discretion of the investigators. Once thrombocytopenia resolves, independent of the mechanism, further administration of CAMPATH-1H will be decided upon by the treating physician and the Study Chair and Co-Chair (Dr. Sanford Kempin and Dr. Neil Kay).

5.1.3.3 The toxicity profile in the two studies (Weiss et al; Kay et al) in which PCR has been used has been modest (see 1.5.2). There has been one grade 5 pulmonary toxicity in the Weiss study and several patients were removed from study (no further details available). The maximum toxicities in the Kay study were grade 3 and no patient has been removed from study. Therefore, it is not anticipated that a significant number of patients will be removed from study during the first phase. Nonetheless, the study toxicity monitors will be notified of any grade 5 event who will then recommend either continuation or stopping of the study. In the studies utilizing the subcutaneous administration of the drug, discontinuation during therapy has been reported.

Discontinuation, however, did not result from grade 4 neutropenia (13%), but rather from severe local reactions (pain) or systemic symptoms (fever, fatigue). Therefore, it is unlikely that the consolidation phase will be prematurely stopped. The main concern on this study is that of microbial infection, particularly CMV reactivation. In view of this, surveillance for CMV will be undertaken at the beginning of each cycle of PCR and every two weeks during CAMPATH-1H. Discovery of reactivation, either because of a clinical syndrome or a laboratory finding, will result in cessation of therapy and treatment of the CMV. A decision to resume therapy after treatment of a CMV event is the responsibility of the principle investigators. If less than grade 4 toxicity has been documented, the protocol may be resumed. If grade 4 toxicity occurs the patient will be removed from study.

5.1.4 Supportive Care Treatment

5.1.4.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.1.4.2 <u>For step 1:</u> All patients must receive daily allopurinol (300 mg/day PO) unless they are allergic and should be well hydrated before the first cycle of PCR treatment is started. All patients will be given PO allopurinol 300 mg/day from day 0 to day 14 (a total of 15 days) for the first month of therapy. Use of allopurinol after this period is discouraged unless the patient has been on this medication chronically. The duration of allopurinol and the need for allopurinol beyond the first cycle is left to the discretion of the treating physician.

Rev. 7/07

5.1.4.3 <u>For step 1 and step 2:</u> Bactrim DS 1 BID on Monday/Wednesday/Friday AND acyclovir 800 mg po BID (or equivalent, including gancyclovir and valgancyclovir) during chemoimmunotherapy (PCR) and immunotherapy (CAMPATH-1H) and for 6 months after completion of this chemoimmunotherapy protocol.

Rev. 12/05
Rev. 7/07

5.1.4.4 <u>For step 1 and step 2:</u> During the induction phase (step 1), G-CSF 300 mcg for patients < 70 kg and 480 mcg for patients > 70 kg will be administered subcutaneously daily beginning two days after each treatment. Neulasta may be used in place of G-CSF, at a dose of 6 mg SQ on day 1 post chemo, Q 4 weeks. At the start of the consolidation (CR, nPR) phase, the absolute neutrophil number is expected to be > 1,000 x 10^6/L. Patients will not be given G-CSF or neulasta routinely unless neutropenia (< 1,000 x 10^6/L) is documented during the weekly follow-up studies. G-CSF or neulasta may be started and maintained to achieve an absolute neutrophil number of > 1,000 x 10^6/L. In the case of G-CSF or neulasta it can be stopped with

Rev. 5/06

two consecutive neutrophil counts of > 1,000 x 10^6/L. For those patients receiving CAMPATH-1H as salvage (PR or PD), the absolute neutrophil number at the start of therapy may be less than 1,000 x 10^6/L and G-CSF or neulasta is recommended to maintain the absolute neutrophil number > 1,000 x 10^6/L during the CAMPATH-1H administration.(If neutropenia persists beyond day 12, G-CSF should be continued until the ANC is > 1 x10^9/L for 2 consecutive blood counts. G-CSF may be discontinued prior to day 12 if ANC is > 1x 10^9/L for 2 consecutive blood counts.)

5.1.4.5 For step 2: Although no fatal toxicity has been seen with SC administration of CAMPATH-1H, life-threatening and fatal CMV disease has been reported with Campath-1H therapy, especially when Campath-1H was used following nucleoside analogs.

Development of rapid methods to diagnose CMV infection before onset of clinical disease has been the main focus of attention in stem cell transplantation. The frequency of infection after cytotoxic therapy utilizing purine analogs and immunologic targets warrants a similar approach. In the transplant setting, older age, the use of purine analogs or monoclonal antibodies directed against T-cells and seropositivity prior to transplantation, are important risk factors for CMV disease and are likely to be operative in the elderly prior-treated CLL population. Various methodologies have been used to diagnose infection. The shell vial culture technique coupled with immunofluorescence assays enables diagnosis within several days. Broncheoalveolar lavage has a sensitivity and specificity of 90%. Blood tests including CMV pp65 antigenemia and PCR techniques detect virus in the blood several weeks before onset of disease, but the former can be quite subjective.

Attempts to prevent infection will depend upon the serologic status of the patient prior to immunosuppressive therapy. For seronegative patients, CMV negative blood products, if needed, are recommended. In seropositive patients, prophylactic use of gancyclovir in the transplant setting has been successful in preventing clinical infection. We do not propose to use this latter strategy in the present protocol. Rather, each patient will remain on acyclovir prophylaxis for the total treatment time and for six months thereafter. Pre-emptive therapy, by serial patient monitoring from the beginning of PCR to the completion of CAMPATH-1H, will be used. For purposes of this study, testing will be performed at the beginning of each cycle of PCR and every two weeks during CAMPATH-1H, utilizing the current methodology at each center (either pp65 antigenemia or CMV DNA by RTPCR). CMV serology must

Rev. 7/07

be obtained as part of baseline studies. Individual centers may define active infection by their own guidelines. In general a positive pp65 result, or a greater than 400-copy result by PCR will define active CMV infection. For patients developing active infection but no clinical sequel, a course of either gancyclovir or valgancyclovir is recommended.

Rev. 7/07

Duration of therapy will be left to each individual center. Individual centers have used three weeks to 12 weeks as duration of therapy. The protocol at each center will be used. Therapy will be interrupted during this period of time. Once monitoring determines absence of active infection, both therapy and continuing monitoring will be resumed.

5.1.5 The potential for toxicity during the induction and consolidation/salvage phases demands prophylactic antibacterial, antifungal and antiviral therapy, monitoring for viral occurrence and provision for stopping therapy if too toxic. Prophylactic antibacterial and antiviral therapy are discussed in Sections 5.1.4. CMV reactivation during both the induction and consolidation/salvage phase will be monitored and verified by polymerase chain reaction assays (86).

5.2 Step 2 (Arm B and Arm C): CAMPATH-1H

Rev. 7/07

5.2.1 Allopurinol will not be administered to patients who have achieved a confirmed CR or nPR. Allopurinol (300 mg/d) will be administered to those patients who have achieved only a PR or SD (or PD) after the PCR regimen. The duration of allopurinol administration will be left to the discretion of the investigator.

Rev. 7/07

5.2.2 For those patients achieving a confirmed CR or nPR, they will be registered to receive CAMPATH-1H (Arm B). When the patient is registered to Arm B, the drug will be administered three times a week for four weeks. The dose will be 30 mg per dose. A twelve-week treatment-free period will elapse before CAMPATH-1H begins following completion of PCR for Arm B patients. Patients will be

Rev. 12/05

assessed with physical examination, CBC, chemistries, and CMV monitoring (see Section 7).

Rev. 7/07

For those patients not achieving a CR or nPR (thus patients have either achieved PR, SD, or PD), CAMPATH-1H (Arm C) will be administered three times a week for eighteen weeks at a dose of 30

Rev. 7/07

mg TIW. For PR, SD and PD patients, the timing of CAMPATH-1H will be left to the discretion of the investigator, and treatment may begin earlier but no less than two weeks and no longer than eight weeks

Rev. 7/07

after the completion of the last PCR course. Patients determined to have PD during treatment with PCR do not need to complete all 6 cycles of PCR to go on to Arm C, however, completing a minimum of

Rev. 12/05, 1/09

2 cycles is required. Patients will be assessed with physical examination, CBC chemistries, and CMV monitoring (see Section 7).

5.2.3 CAMPATH-1H will be administered subcutaneously in a volume of 1.5 ml (55). CAMPATH-1H will be initially administered at a dose of 3 mg by subcutaneous injection in the thigh (day 1). The dose will be increased to 10 mg on day 3 and then raised to 30 mg on day 5. If > grade 2 toxicity occurs do not increase dose until toxicity returns to grade 1 or less.

Agent	Dose	Route	Initial Response	Duration	Frequency
CAMPATH-1H	30 mg	SQ	CR/nPR	4 weeks	TIW
CAMPATH-1H	30 mg	SQ	PR/PD	18 weeks	TIW

5.2.4 Premedications will consist of acetaminophen 650 mg po and diphenhydramine 50 mg PO 30 minutes prior to each injection during the first week. Thereafter, acetaminophen and diphenhydramine will be administered according to the discretion of the investigator. Additional therapy will be left to the discretion of the treating physician but should not include corticosteroids.

5.2.5 During the period of CAMPATH-1H administration, anti-infective prophylaxis is essential. Trimethoprim/sulfamethoxazole (Bactrim) DS 1 (BID) Monday, Wednesday and Friday, and acyclovir 800 mg BID will be administered for the 4-week and 18-week course of treatment and for six months after completion of treatment. For patients allergic to Trimethoprim/sulfamethoxazole (Bactrim), Dapsone may be used instead at a dose of 100 mg PO QD.

Rev. 12/05, 1/09

Rev. 1/09

Rev. 12/05 5.2.6 For those patients entering the consolidation phase in CR or nPR, the absolute neutrophil number is expected to be above 1,000 $x10^6$/L. Patients will not be given G-CSF (or neulasta) routinely unless neutropenia (≤ 1,000 $x10^6$/L) is documented during the weekly follow-up studies. G-CSF (or neulasta) may be started and maintained to achieve a neutrophil number > 1,000 $x10^6$/L. For those patients receiving CAMPATH-1H in PR, SD, or during PD (salvage phase), the absolute neutrophil number may be less than 1,000 $x10^6$/L and G-CSF (or neulasta) is recommended to maintain the neutrophil number > 1,000 $x10^6$/L during the CAMPATH-1H administration.

5.2.7 Although grade 4 toxicity, other than myelosuppression is not expected to occur during the CAMPATH-1H administration, the following side effects should be considered by the investigator as possible causes of removal from study: prolonged neutropenia, severe febrile course, severe eczema and the appearance of autoimmune phenomena (thyroiditis, anemia, thrombocytopenia).

Rev.8/05,1/09 1/09 5.2.8 There will be no dose modification for CAMPATH-1H. However, if grade 4 non-hematologic toxicity occurs due to CAMPATH-1H the investigator may remove the patient from study if the risks outweigh the benefits (see 5.2.7). Grade 4 hematologic toxicity is unusual but may result in such morbidity that the investigator feels the subject should be removed from the study. The decision to remove a patient from study in these circumstances should be discussed with the principal investigator prior to removal.

Rev. 8/05, 6/14

5.3 ADVERSE EVENT REPORTING REQUIREMENTS

5.3.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E2903 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.3.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

Steps to determine if an adverse event is to be reported in an expedited manner:

Rev. 5/11

Step 1: *Identify the type of event:* The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until June 30, 2011 for AE reporting. CTCAE version 4.0 will be utilized beginning July 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Step 2: *Grade the event using the NCI CTCAE version 4.0*.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is **NOT** listed in:

- **Arm A, B, and C** – the drug package insert or protocol

Step 5: Review Section 5.3.6 for E2903 and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

Rev. 1/14

5.3.3 Reporting methods

Arm A B or C - This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617 632 2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.3.4 When to report an event in an expedited manner

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section 5.3.6.

NOTE: Adverse events that meet the reporting requirements in Section 5.3.6 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Section 5.3.6 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.3.5 Other recipients of adverse event reports

Adverse events determined to be reportable must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

The drug supporter is obliged to forward reported AEs to the FDA. A drug supporter representative may call a site for additional information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

5.3.6 Expedited reporting for commercial agents

Commercial reporting requirements are provided below. The commercial agents used in arms A, B, and C of this study are Pentostatin, Cyclophosphamide, Rituximab, and Campath-1H.

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arm A, B and C

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution.

NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Hepatitis B Virus: All cases of Hepatitis B Virus (HBV) reactivation with fulminant hepatitis and hepatic failure must be reported via CTEP-AERS within 7 calendar days of learning of the event.

Rev.1/09

Protocol Specific Reporting Requirements

Rev.1/09

Rev. 5/06

All ≥ Grade 3 events felt to be possibly, probably or definitely related to protocol treatment (regardless of expectedness) must be reported via CTEP-AERS within 7 calendar days of learning of the event.

Rev. 1/14

5.3.7 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office - Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215
  2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office - Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated

pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. 5/10

5.3.8 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Alemtuzumab (NSC 715969)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR(s) below, as well as the other resources described in the 'Determination of reporting requirements' part of the Adverse Event Reporting section in this protocol, can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS. *Frequency is provided based on 346 patients.* Below is the CAEPR for alemtuzumab.

Version 2.1, March 23, 2010[1]

Adverse Events with Possible Relationship to Alemtuzumab (CTCAE 4.0 Term) [n= 346]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
		Blood and lymphatic system disorders - Other (bone marrow aplasia)
	Disseminated intravascular coagulation	
	Febrile neutropenia	
		Hemolysis
CARDIAC DISORDERS		
	Atrial fibrillation	
	Cardiac arrest	
		Left ventricular systolic dysfunction
	Myocardial infarction	
	Sinus tachycardia	
	Ventricular arrhythmia	
	Ventricular tachycardia	
ENDOCRINE DISORDERS		
	Hyperthyroidism	
	Hypothyroidism	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
	Diarrhea	
	Dyspepsia	
	Mucositis oral	
Nausea		
	Small intestinal mucositis	
Vomiting		

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Chills		
	Edema limbs	
Fatigue		
Fever		
	Flu like symptoms	
	Injection site reaction	
	Non-cardiac chest pain	
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
	Autoimmune disorder	
	Cytokine release syndrome	
	Serum sickness	
INFECTIONS AND INFESTATIONS		
	Infection[2]	
Infections and infestations – Other (Opportunistic infection with ≥Grade 2 Lymphopenia)		
INVESTIGATIONS		
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
Lymphocyte count decreased		
Neutrophil count decreased		
Platelet count decreased		
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hypoalbuminemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthritis	
	Back pain	
	Generalized muscle weakness	
	Myalgia	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Dysgeusia	
	Headache	
	Peripheral sensory neuropathy	
PSYCHIATRIC DISORDERS		
	Insomnia	

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Allergic rhinitis	
	Bronchospasm	
	Cough	
	Dyspnea	
	Hypoxia	
	Pneumonitis	
	Pulmonary edema	
	Stridor	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus	
	Purpura	
	Rash acneiform[3]	
	Urticaria	
VASCULAR DISORDERS		
	Flushing	
	Hypertension	
	Hypotension	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Also may include desquamation.

[4]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

Also reported on alemtuzumab trials but with the relationship to alemtuzumab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy)

CARDIAC DISORDERS - Pericarditis

EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus

ENDOCRINE DISORDERS - Endocrine disorders - Other (aggravated diabetes mellitus)

EYE DISORDERS - Optic nerve disorder

GASTROINTESTINAL DISORDERS - Ascites; Colitis; Gastrointestinal hemorrhage[4]; Gastrointestinal perforation[5]; Gastrointestinal ulcer[6]; Pancreatitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Gait disturbance; General disorders and administration site conditions - Other (Goodpasture's syndrome); General disorders and administration site conditions - Other (Guillain-Barre syndrome); General disorders and administration site conditions - Other (Hemophagocytic syndrome); General disorders and administration site conditions - Other (Syndrome of Inappropriate Antidiuretic Hormone Secretion [SIADH])

INVESTIGATIONS - Blood bilirubin increased; Creatinine increased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hypocalcemia; Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Joint range of motion decreased; Musculoskeletal and connective tissue disorder - Other (muscle atrophy); Myositis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Seizure; Syncope

PSYCHIATRIC DISORDERS - Agitation; Depression; Personality change; Psychosis

RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (toxic nephropathy); Urinary frequency; Urinary retention; Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Reproductive system and breast disorders - Other (cervical dysplasia); Reproductive system and breast disorders - Other (ovarian failure)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchial obstruction; Bronchopulmonary hemorrhage; Pulmonary fibrosis

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme

VASCULAR DISORDERS - Vascular disorders - Other (increased capillary fragility); Vascular disorders - Other (splenic infarction)

NOTE: Alemtuzumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Rev. 6/10

5.3.9 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Rituximab (NSC 687451)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR(s) below, as well as the other resources described in the 'Determination of reporting requirements' part of the Adverse Event Reporting section in this protocol, can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS. Frequency is provided based on 986 patients. Below is the CAEPR for Rituximab.

Version 2.1, March 19, 2010[1]

Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n= 986]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Blood and lymphatic system disorders - Other (Hyperviscosity: Waldenstrom's)	
	Febrile neutropenia	
CARDIAC DISORDERS		
	Myocardial infarction	
	Sinus tachycardia	
	Supraventricular tachycardia	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Diarrhea	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Chills		
	Edema limbs	
	Fatigue	
Fever		
Infusion related reaction		
	Pain	
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis
	Serum sickness	

INFECTIONS AND INFESTATIONS		
	Infection[2]	
	Infections and infestations - Other (Activation of Hepatitis B, C, CMV, parvovirus B19, JC virus, varicella zoster, herpes simplex, West Nile virus)	
	Infections and infestations - Other (Infection in HIV Positive Patients)	
INVESTIGATIONS		
Lymphocyte count decreased		
	Neutrophil count decreased	
	Platelet count decreased	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Hyperglycemia	
	Hypocalcemia	
	Hypokalemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Myalgia	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	Tumor pain	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
	Lethargy	
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)
	Seizure	
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Adult respiratory distress syndrome
	Allergic rhinitis	
	Bronchospasm	
	Cough	
	Dyspnea	
	Hypoxia	
	Pneumonitis	
	Sore throat	

SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
	Skin and subcutaneous tissue disorders - Other (angioedema)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
	Urticaria	
VASCULAR DISORDERS		
	Flushing	
	Hypertension	
	Hypotension	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

Also reported on rituximab trials but with the relationship to rituximab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Hemolysis

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (cyanosis); Left ventricular systolic dysfunction; Sinus bradycardia; Ventricular fibrillation

EYE DISORDERS - Conjunctivitis; Eye disorders - Other (ocular edema); Uveitis; Watering eyes

GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Dysphagia; Gastrointestinal obstruction[3]; Gastrointestinal perforation[4]; Mucositis oral

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=Grade 2 Lymphopenia)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture

INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Investigations - Other (hyperphosphatemia); Investigations - Other (LDH increased); Weight loss

METABOLISM AND NUTRITION DISORDERS - Anorexia; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoglycemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis

NERVOUS SYSTEM DISORDERS - Nervous system disorders - Other (Cranial Neuropathy NOS); Peripheral motor neuropathy; Peripheral sensory neuropathy; Pyramidal tract syndrome; Reversible posterior leukoencephalopathy syndrome; Syncope

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Depression; Insomnia

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Pharyngolaryngeal pain; Pleural effusion; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Skin and subcutaneous tissue disorders - Other (paraneoplastic pemphigus)

VASCULAR DISORDERS - Phlebitis; Thromboembolic event; Vasculitis

NOTE: Rituximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4 Duration of Therapy

5.4.1 There is a significant potential for this regimen to be exceedingly immunosuppressive and toxic. For that reason careful monitoring of side effects and prophylaxis against microbial infection is essential (see Section 5.1.4).

Rev. 7/07

5.4.2 Patients achieving a clinical CR will not have a confirmed CR or nPR until the initial post treatment bone marrow biopsy and aspirate is done 8 weeks after determining a clinical CR. Patients with a confirmed CR or nPR at 12 weeks after 6 cycles PCR treatment, will be treated with Campath-1H 30 mg, TIW for 4 weeks (see Section 7).

Rev. 7/07

5.4.3 Patients achieving PR or those who achieve less than a PR after 6 cycles of PCR will receive a full 18 week course of CAMPATH-1H at 30 mg SQ TIW.

Rev. 7/07

Rev. 1/09

5.4.4 Patients demonstrating progression while on PCR can register for the full 18 week course of CAMPATH-1H, Arm C. They do not have to complete all 6 cycles of PCR but must have completed at least 2 cycles.

5.4.5 Patients will receive protocol therapy unless:

5.4.5.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the E2903 Forms Packet.

5.4.5.2 Patient withdraws consent.

5.4.5.3 If treatment is discontinued due to patient refusal or noncompliance, unacceptable toxicity or intercurrent illness that makes treatment assessment difficult, patients will be observed until they relapse ***and*** require chemotherapy.

5.4.5.4 If disease progression occurs during the CAMPATH-1H treatment, treatment will be discontinued.

5.4.5.5 Active HBV infection or hepatitis develops.

5.5 Duration of Follow-up

5.5.1 For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression and for survival for 5 years from the date of registration.

6. Measurement Of Effect

(See Appendix VII)

6.1 Assessment of Clinical Response

Rev. 7/07

The major criteria for determination of the response to therapy in patients with B-CLL include physical examination and evaluation of peripheral blood and bone marrow (if evaluating for CR). It is recommended that the laboratory and physical exam findings, which are abnormal prestudy, be repeated to document the degree of maximal response.

Rev. 7/07

Measurements of the largest **palpable** lymph nodes (provide measurements on a minimum of 2 of the largest nodes but no more than 5) should be selected at baseline to be followed for response. These lymph nodes should be clearly measurable in two perpendicular dimensions and should be selected from each of the following sites, if involved: cervical, supraclavicular, axillary, inguinal, femoral.

Rev. 7/07

6.1.1 A clinical complete remission requires all of the following for a period of at least 8 weeks:

Rev. 7/07

6.1.1.1 Absence of lymphadenopathy by physical examination.

Rev. 7/07

6.1.1.2 No hepatomegaly or splenomegaly. Spleen and/or liver, if considered enlarged at baseline, should not be palpable, due to disease, on physical exam.

6.1.1.3 Absence of constitutional symptoms, as described in Section 3.1.2.1.

Rev. 7/07

6.1.1.4 Normal CBC as exhibited by:

6.1.1.4.1 Polymorphonuclear leukocytes $\geq$ 1500 x 10^6/L

6.1.1.4.2 Platelets > 100,000 x 10^6/L

6.1.1.4.3 Hemoglobin > 11.0 gm/dl (untransfused)

6.1.1.4.4 Peripheral blood lymphocytes $\leq$ 4000 x 10^6/L

Rev. 7/07

Rev. 7/07

6.1.2 Confirmed Complete Remission or nPR

Confirmed complete remission requires all of Section 6.1.1 and a normal bone marrow as defined below.

One marrow aspirate and biopsy should be performed no sooner than 8 weeks after clinical CR has been documented. The marrow sample must be at least normocellular with $\leq$30% of nucleated cells being lymphocytes. If it is hypocellular, a repeat determination should be made in 2 weeks. Samples are to be analyzed by a pathologist and the presence or absence of nodules noted.

A patient who is in CR, but has nodules, will be considered to have nodular PR (nPR) and recorded separately.

If no confirmatory bone marrow biopsy is done in the specified time period, or if the bone marrow biopsy shows evidence of disease, the response will be PR.

Any other laboratory assays (e.g. quantitative immunoglobulins) will not be used currently as an index for response but will be recorded for clinical correlations.

6.1.3 Partial Response or PR

Rev. 7/07

To be considered in PR, the patient must exhibit the features in Sections 6.1.3.1 – 6.1.3.3 and one or more of the following features in Section 6.1.3.4 – 6.1.3.6 for at least 8 weeks. In addition to the parameters listed below, the presence or absence of constitutional symptoms will be recorded. Because the PR can be defined during the course of treatment, it is necessary to document a physical exam

Rev. 7/07

including assessment of liver and spleen, measurement of lymphadenopathy and hematologic evaluation (CBC, differential and platelet count) every cycle during treatment.

6.1.3.1 >50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.

6.1.3.2 > 50% reduction in lymphadenopathy.

Rev. 7/07

6.1.3.3 No increase in size of liver and/or spleen.

6.1.3.4 Polymorphonuclear leukocytes > 1500 x 10^6/L or 50% improvement over baseline.

6.1.3.5 Platelets >100,000 x 10^6/L or 50% improvement over baseline.

6.1.3.6 Hemoglobin >11.0 gm/dl or 50% improvement over baseline without transfusions.

NOTE: Patients in clinical complete remission but with evidence of disease in the bone marrow will be a PR.

6.1.4 Progressive disease (PD) will be characterized by at least one of the following:

Rev. 7/07

6.1.4.1 > 50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive examinations 2 weeks apart (at least 1 node must be > 2 cm). Appearance of new palpable lymph nodes > 1 cm.

Rev. 7/07

6.1.4.2 Increase in the size of liver and/or spleen, as determined by physical exam, below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.

6.1.4.3 > 50% increase in the absolute number of circulating lymphocytes.

6.1.4.4 Transformation to a more aggressive histology (e.g. Richter's syndrome or prolymphocytic leukemia with >55% prolymphocytes).

6.1.4.5 In the absence of progression as defined above, the presence of a > 2 gm/dl decrease in hemoglobin, or > 50% decrease in platelet count and/or absolute granulocyte count will not exclude a patient from continuing on study. Bone marrow aspirate and biopsy are strongly encouraged to better define the cause of the suppressed counts.

6.1.4.6 Patients who have not achieved a CR, nPR or PR or who have not exhibited findings consistent with Progressive disease will be considered as having Stable Disease.

7. Study Parameters

Rev. 7/07

7.1 Therapeutic Parameters

1. Chest x-rays should be done ≤ 30 days before registration.
2. Prestudy CBC with differential, LFTs should be done ≤ 2 weeks before registration.
3. All required prestudy chemistries should be done ≤ 2 weeks before registration - unless specifically required on Day 1 as per protocol. If abnormal, they must be repeated within 48 hours prior to registration.
4. Prestudy Hgb, Hct, WBC, Plt should be done ≤ 2 weeks before registration.

Rev. 8/05
Rev. 8/05
Rev. 7/07

NOTE: When recording prestudy results on the baseline data form, please make sure that ALL relevant dates are clearly given. Do ***not*** put all the results under the date for Day 1 of protocol treatment unless they were actually done that day. Record the actual dates.

Table 7.1.1

Test Schedule: Pre-treatment and during treatment with PCR (Arm A)

Test/procedures	PRETREATMENT		DURING TREATMENT-PCR (Arm A) [10]		
	Within 30 days prior to registration	Within 14 days prior to registration	Day 1, Cycle 1	Subsequent cycles	8 weeks After Cycle 6
History and exam, height,[6] weight, PS	X		X	X	X
Tumor Measurement by PE	X[3]			X[3]	X[3]
CBC/diff/blood smear		X	Day 1[8], End of Weeks 1-4	Day 1[8], End of Week 2	X
Chem group (SGOT, t bili, creat[11], glucose, calcium, alk phos, albumin, electrolytes, BUN, LDH, uric acid)		X	Day 1[8]	Day 1[8]	X
Chest x-ray	X				X
Screening of patients for HBV infection	X[7]				
[Deleted in Addendum #10]					
Bone Marrow BX/Aspirate	X[2]				X[5]
Pregnancy test		X[1, 4]			
Immunofixation-Beta-2-microglobulin	X				X
Coombs, serum Immunoglobulins	X				X
CMV testing			X[9]	X[9]	

Rev. 1/09
Rev. 7/07
Rev. 8/05, 7/07
Rev. 6/05, 8/05, 5/06
Rev. 6/05, 1/09
Rev. 6/05
Rev. 7/07
Rev. 8/05

1. For women of childbearing potential.
2. Bone marrow biopsy is required.

Rev. 7/07

3. Tumor measurements to be taken at pretreatment, after each cycle through cycle 6. For each visit, physical examination should record the two perpendicular dimensions for each of the palpable lymph nodes assessed at baseline. (Provide measurements on a minimum of 2 of the largest nodes but no more than 5.) Physical exam should also document splenomegaly and hepatomegaly.
4. Only required at on-study.

Rev. 7/07

5. As indicated to assess complete response. CR demonstrated by bone marrow biopsy must be done no sooner than 8 weeks after clinical CR has been documented to confirm that a complete remission has been achieved and sustained.
6. Start of protocol only.
7. LFTs will be monitored monthly until 12 months from the last rituximab dose for patients who test positive for HBV at pretreatment.

Rev. 6/05

8. To be obtained within 24 hours prior to each cycle of treatment.

Rev. 8/05

9. CMV testing to be performed at the beginning of each treatment cycle of PCR and every two weeks during CAMPATH-1H.

Rev. 1/09

10. If patient does not go onto Step 2, CMV testing will be done every 6 months for one year after completion of treatment.

Rev. 1/09

11. Refer to Sec. 5.1.3.1.1 if creatinine clearance is greater than 1.5 but ≤ 2 mg/dl.

Rev. 6/05, 7/07, 1/09

Table 7.1.2

Test Schedule: During and Post-Treatment with CAMPATH-1H - CR/nPR (Arm B)[1]

Test/procedures	CAMPATH – 1H (CR/nPR)[1] (Arm B)				
Rev. 8/05, 7/07	Within 14 days prior to re-registration	Q 2 weeks until completion	Q 4 weeks	Post-treatment at 6 weeks after Day 1 (CR/nPR)	Post-treatment to 5 years from study entry[3]
Rev. 1/09 History and exam, weight, PS	X		X	X	X
Rev. 8/05, 7/07, 1/09 Tumor Measurement by PE	X[2]		X[2]	X[2]	X[2]
Rev. 7/07, 1/09 CBC/diff/blood smear	X		X	X	X
Rev. 8/05, 12/05, 7/07, 1/09 Chem group (SGOT, t billi, creat, glucose, calcium, alk phos, albumin, electrolytes, BUN, LDH, uric acid)	X		X	X	X
Rev. 8/05, 7/07 [Deleted in Addendum #10]					
Rev. 8/05 CMV testing		X[6]			X[7]
Chest x-ray				X	X[4]
Rev. 7/07 [Deleted in Addendum #10]					
Rev. 7/07 Rev. 1/09 Bone Marrow BX/Aspirate				X	X[5]
Immunofixation-Beta-2-microglobulin				X	X[4]
Coombs, serum Immunoglobulins				X	X[4]

1. See Section 5.2 describing the time frame of Campath-1H.
2. For each visit, physical examination should record the two perpendicular dimensions for each of the palpable lymph nodes assessed at baseline. (Provide measurements on a minimum of 2 of the largest nodes but no more than 5.) Physical exam should also document splenomegaly and hepatomegaly. (Rev. 7/07)
3. To begin after the 6-week post-treatment tests: Every 3 months if patient is ≤ 2 years from study entry and every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is more than 5 years from study entry.
4. To be done yearly to 5 years from study entry.
5. Every 6 months from completion of study. If at any time prior to the 6-month follow-up an abnormality is noted, either clinically (lymphadenopathy, splenomegaly) or by blood tests suggesting relapse (lymphocytosis), a bone marrow study will be performed.
6. CMV testing to be performed at the beginning of each treatment cycle of PCR and every two weeks during CAMPATH-1H. (Rev. 8/05)
7. CMV testing will be done every 6 months for one year after completion of treatment. (Rev. 7/07 Rev. 1/09)

NOTE: LFTs will be monitored until 12 months from the last rituximab dose for patients who test positive for HBV at pretreatment (see table 7.1.1)

Rev. 6/05, 7/07, 1/09

Table 7.1.3

Test Schedule: During and Post-Treatment with Campath-1H – PR/SD/PD (Arm C) [1]

Rev. 8/05 Test/procedures	CAMPATH-1H – (PR/SD/PD)[1] (ARM C)				
	Within 14 days prior to re-registration	Q 2 weeks until completion	Q 4 weeks until completion	Post-treatment at 6 weeks after Day 1 (CR/nPR)	Post-treatment to 5 years from study entry[3]
Rev. 1/09 History and exam, weight, PS	X		X	X	X
Rev. 8/05, 1/09 Tumor Measurement by PE	X[2]		X[2]	X[2]	X[2]
Rev. 1/09 CBC/diff Blood smear	X		X	X	X
Rev. 8/05, 12/05, 1/09 Chem group (SGOT, t billi, creatinine[7], glucose, calcium, alk phos, albumin, electrolytes, BUN, LDH, uric acid)	X		X	X	X
Rev. 8/05, 12/05, 7/07 [Deleted in Addendum #10]					
Chest x-ray	X			X	X[4]
Rev. 7/07 [Deleted in Addendum #10]					
Rev. 7/07 Rev. 1/09 Bone marrow asp/bx				X	X[5]
Immunofixation – Beta-2-microglobulin	X			X	X[4]
Coombs, Serum Immunoglobulins	X			X	X[4]
Rev. 8/05 CMV testing		X[5]			X[6]

Rev. 1/09 1. See Section 5.2 describing the time frame of CAMPATH-1H.

Rev. 7/07 2. For each visit, physical examination should record the two perpendicular dimensions for each of the palpable lymph nodes assessed at baseline. (Provide measurements on a minimum of 2 of the largest nodes but no more than 5.) Physical exam should also document splenomegaly and hepatomegaly.

Rev. 7/07 3. Every 3 months if patient is ≤ 2 years from study entry and every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is more than 5 years from study entry.

4. Every 6 months from completion of study. If at any time prior to the 6-month follow-up an abnormality is noted, either clinically (lymphadenopathy, splenomegaly) or by blood tests suggesting relapse (lymphocytosis), a bone marrow study will be performed.

Rev. 8/05 5. CMV testing to be performed at the beginning of each treatment cycle of PCR and every two weeks during CAMPATH-1H.

Rev. 7/07 6. CMV testing will be done every 6 months for one year after completion of treatment.

Rev. 1/09 7. **NOTE:** May be calculated using the Cockcroft-Gault Equation: (140-age)*wt(kg)/([Cr]*72) For women the calculation may be multiplied by 0.85.

NOTE: LFTs will be monitored until 12 months from the last rituximab dose for patients who test positive for HBV at pretreatment (see table 7.1.1)

7.2 Biological Sample Submissions

1. Submission of peripheral blood for immunophenotypic diagnostic review is **mandatory**. Failure to submit the materials may render the patient unevaluable. See Section 11.1
2. Samples for the optional correlative studies and banking should be submitted as outlined in Sections 11.2 and 11.3. Collection of samples should be limited to those patients who have given written informed consent to participate in the correlative studies.

Rev. 5/06

NOTE: An informed consent MUST be signed prior to the submission of any material for any correlative study, including mandatory diagnostic reviews. Samples for optional correlative studies should be submitted only from patients who have given written consent for the use of their samples for these purposes.

Rev. 1/09

NOTE: For patients who consent to the laboratory studies, please submit ALL sequential blood specimens at ALL time points.

Parameters	Baseline	After PCR	After CAMPATH-1H or Discontinuation of Protocol Treatment	Q 6 months[2]	Time of Response assessment	Ship to:
Peripheral Blood (green top)[1]	**2 tubes[1]**					Dr. Paietta (Section 11.1)
Peripheral Blood (red top)	1 tube					
Peripheral Blood (green top)	1 tube	1 tube	1 tube			Cytogenetics Lab (Section 11.2)
Peripheral Blood (green top)	10 tubes	5 tubes	5 tubes	5 tubes		Mayo Clinic (Section 11.3)
Peripheral Blood (red top)	1 tube	1 tube	1 tube	1 tube		
Marrow Slides/Tissue[3]	X	X	X		X[3]	

Rev. 5/06

1. Submission mandatory for diagnostic review. Samples should be submitted as indicated in Section 11.1. Samples should be collected after registration prior to beginning therapy.
2. Samples are requested at baseline, after completion of PCR, after completion of Campath, and every six months following therapy for 5 years from start of therapy.

Rev. 1/09

3. Bone marrow block or 8-10 unstained, positively charged slides are requested. Sample should be submitted at any time a BM is performed to assess response.

8. Drug Formulation and Procurement

8.1 Cyclophosphamide

8.1.1 Other Names

Cytoxan, Neosar, CTX, CPM

8.1.2 Classification

Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system.

8.1.3 Mode of Action

Cyclophosphamide metabolites are thought to disrupt cell division primarily by cross-linking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific.

8.1.4 Storage and Stability

Injectable powder are stored at room temperature 25°C (77°F). The temperature is not to exceed 30°C (90 F°). Reconstituted parenteral solutions are stable for 24 hours at room temperature for 6-14 days if refrigerated.

8.1.5 Dose Specifics

Rev. 5/06

600 mg/m^2/day on day 1 of weeks 1, 5, 9, 13, 17, and 21.

8.1.5.1 Dosage in Renal or Hepatic Failure

Cyclophosphamide dosage adjustment for patients with renal or hepatic failure has not been adequately evaluated.

8.1.6 Preparation

Dissolve the 100 mg, 200 mg, 500 mg, 1 gm, and 2 gm vials in 5, 10, 25, 50, and 100 ml of sterile water, respectively, resulting in a solution of 20 mg/ml. Shake vials vigorously and warm slightly in lukewarm water to facilitate dissolution. The lyophilized form is more easily solubilized.

Reconstituituted solutions may be further diluted in D5W, D5W/NS, D5W/Ringer's Injection, Lactated Ringer's Injection, and ½ NS.

8.1.7 Administration

To be given by IV.

8.1.8 Compatibilities

Numerous compatibility studies have been published. For specific details refer to handbook on injectable drugs by Lawrence A. Trissel (sec. 8.1.13).

8.1.9 Availability

Cyclophosphamide is commercially available for parenteral injection as 100 mg, 200 mg, 500 mg, 1 g, and 2 g vials.

8.1.10 Side Effects – Please refer to package insert.

Side effects vary significantly based on the specific dose and duration of cyclophosphamide.

8.1.10.1 Incidence More Frequent (> 5%)

1. Anemia, leukopenia (usually asymptomatic; less frequently fever and/or chills)
2. Thrombocytopenia (usually asymptomatic; less frequently unusual bleeding or bruising; black tarry stools; blood in urine or stools; pinpoint red spots on skin). Nadir counts usually occur 7 to 12 days after administration and recovery usually compete by day 17 to 21.
3. Alopecia
4. Anorexia, nausea and vomiting
5. Gonadal suppression (azoospermia, missed menstrual periods) resulting in infertility. Return of normal gonadal function and fertility occurs with time in many younger men and women.
6. Hemorrhagic cystitis

8.1.10.2 Incidence Less Frequent (1-5%)

1. Stomatitis

8.1.10.3 Incidence Rare (1%)

1. Anaphylaxis (tachycardia, shortness of breath, wheezing, tightness in throat)
2. Flushing or redness of face
3. Diarrhea
4. Skin rash
5. Pneumonitis or interstitial pulmonary fibrosis
6. Syndrome of inappropriate antidiuretic hormone (siadh)
7. Chemical phlebitis (redness, swelling or pain at site of injection)
8. Secondary malignancies
9. Blurred vision, cardiac toxicity presenting as congestive heart failure
10. Hemorrhagic myocarditis
11. Cardiac necrosis
12. Pericarditis (seen with high dose regimens used with bone marrow transplantation)

8.1.11 Drug Interactions

8.1.11.1 Digoxin

Several studies conducted in lymphoma patients receiving combination chemotherapy including cyclophosphamide revealed a 20–50% reduction in digoxin absorption when

digoxin tablets were administered. When digoxin capsules were administered no significant decrease in digoxin absorption occurred. To avoid decreased serum digoxin levels the use of digoxin in liquid form (liquid or capsules containing liquid digoxin) instead of tablets is recommended.

8.1.11.2 Pentostatin

Two case reports describe fatal cardiac toxicity in patients receiving cyclophosphamide 6.4 g/m² over 4 days and pentostatin 4 mg/m² over 4 hours on day 3.

8.1.11.3 Succinylcholine

Cyclophosphamide may prolong the effects of succinylcholine by irreversibly inhibiting the enzyme pseudocholinesterase. Limited clinical observations and *in vitro* studies suggest that prolonged apnea might result when succinlycholine is administered to some patients also receiving cyclophosphamide. Management options include avoiding concurrent therapy or if concurrent therapy can not be avoided, to monitor for prolonged succinlycholine effect in patients receiving both drugs. If cyclophosphamide has been administered within 10 days of succinylcholine, extreme caution should be used after succinylcholine administration. The anesthesiologist should be informed of the potential for succinylcholine-induced apnea and appropriate precautions and monitoring should be implemented.

8.1.11.4 Trastuzumab

In early clinical trials the concurrent administration of cyclophosphamide and trastuzumab increased the incidence and severity of cardiac dysfunction. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended.

8.1.12 Nursing/Patient Implications

1. Monitor CBC, platelet count. Advise patients of increased risk of infection with absolute neutrophil count less than 500 cells/mm³ and increased risk of bleeding with platelet counts less than 20,000 cells/ mm³. Advise patients to call the clinic if they develop a fever above 101°F or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
2. Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.
3. Assess hydration and fluid balance. Patients receiving larger doses should force fluids up to 2 liters above normal intake for 72 hours after administration. Instruct patients to void more

frequently to minimize occurrence of hemorrhagic cystitis. For high-dose therapy MESNA may be used.

4. Premedicate with antiemetics.
5. Observe for possible phlebitis at injection site.
6. Administer antiemetics as indicated.

8.1.13 References

American Hospital Formulary Service 99 – Drug Information; 832-837.

Cytoxan Package Insert, Princeton, NJ: Mead Johnson Oncology Products 1998; July Micromedex Inc. Vol. 101; 1999.

USPDI Volume 1 1999; 1128-1134.

Trissel L.A, Handbook on injectable drugs (8th Ed), Bethesda, MD: American Society of Hospital Pharmacists, 1994, Pp. 287-295.

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Gryn *et. al.* Pentostatin increases the acute toxicity of high dose cyclophosphamide. Bone Marrow Transplantation 1993; 12:217-220.

Pedersen-Bjergaard J, Ersboll J, Sorenson HM. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for Non-Hodgkin's lymphoma. Ann Intern Med 1985; 103:195-200.

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Zucchero FJ, Ed. Evaluation of drug interactions. St. Louis: Professional Drug Systems, 1997; 2/35, 12/21.

Hansten Pd, Ed. Drug interactions analysis and management. Applied Therapeutics, Inc., Vancouver, WA 1998; 185-186.

Trastuzumab Package Insert, South San Francisco, CA Genentech, Inc. 1998; September.

Date/Reviewer: July 1999/Robert K. Sylvester, PharmD (701) 234-5154.

8.2 Pentostatin

8.2.1 Other Names

Nipent, 2'-Deoxycoformycin, dCF, Co-Vidarabine, NSC # 218321.

8.2.2 Classification

Adenosine deaminase inhibitor (antimetabolite).

8.2.3 Mode of Action

Adenosine deaminase (ADA) is an enzyme that is essential for the metabolism of purine nucleosides. Pentostatin irreversibly inhibits ADA activity resulting in intracellular accumulation of adenosine and

deoxyadenosine, leading to cell death. Other proposed mechanisms of cytotoxicity include depletion of adenosine triphosphate (reducing cellular energy levels and cyclic adenosine monophosphate formation), incorporation of the triphosphate of pentostatin into DNA, and formation of DNA strand breaks.

8.2.4 Storage and Stability

Unreconstituted drug vials are stored in the refrigerator. Reconstituted solutions (2 mg/ml) are chemically stable at room temperature for at least 72 hours. Dilute solutions (10 mg/500 ml) are chemically stable at room temperature for 24 hours in 5% dextrose, 48 hours in normal saline or lactated Ringer's. Refrigerated solutions are chemically stable for at least 96 hours.

8.2.5 Dose Specifics

Rev. 5/06

4 mg/m²/day on day 1 of weeks 1, 5, 9, 13, 17, and 21.

8.2.6 Preparation

The 10 mg vial is reconstituted with 5 ml of normal saline, resulting in a 2 mg/ml solution. The desired dose is further diluted to concentrations of 1 mg/ml or less in normal saline, lactated Ringer's or 5% dextrose.

8.2.7 Administration

Pentostatin is usually administered by IV bolus, over 2 minutes or longer. Patients should be hydrated with 500-1000 ml fluid (D5W, 0.5NS, or equivalent), prior to administration, and another 500 ml should be administered afterward.

8.2.8 Incompatibilities

No information available.

8.2.9 Availability

Pentostatin, 10 mg/vial, is commercially available.

8.2.10 Side Effects – Please refer to package insert.

1. Hematologic: Leukopenia, thrombocytopenia, lymphopenia, anemia, infections.
2. Dermatologic: Rash, dry skin.
3. Gastrointestinal: Nausea, vomiting, stomatitis, diarrhea, anorexia, altered taste.
4. Hepatic: Elevated liver enzymes, rarely hepatitis, elevated LDH, hyperbilirubinemia.
5. Neurologic: Lassitude, confusion, expressive aphasia, slurred speech, depression, hallucinations, agitation, cerebral edema, seizures, coma; dose-limiting in phase I studies, but the more severe toxicities occur rarely with conventional doses (i.e., 4 mg/m² every 2 weeks).
6. Pulmonary: Cough, shortness of breath, respiratory insufficiency, pulmonary infiltrates on chest X-ray.

7. Renal: Elevated serum creatinine; acute tubular necrosis; renal failure.
8. Other: Keratoconjunctivitis, photophobia, fever, arthralgia, myalgia; severe and fatal infections have been reported.

8.2.11 Nursing/Patient Implications

1. Monitor CBC, platelet counts.
2. Administer antiemetics as indicated.
3. Assess for neurologic toxicities.
4. Monitor for symptoms of pulmonary toxicity.
5. Observe for rash, dry skin.
6. Monitor for diarrhea, stomatitis, and treat symptomatically.

8.2.12 References

Grever MR, Leiby JM, Kraut EH, *et al.* Low-dose deoxycoformycin in lymphoid malignancy. J Clin Oncol 1985; 3: 1196-1201.

O'Dwyer PJ, Wagner B, Leyland-Jones B, *et al.* 2'-Deoxycoformycin (pentostatin) for lymphoid malignancies. Rational development of an active new drug. Ann Intern Med 1988; 108: 733-743.

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O'Dwyer PJ, Spiers AS, Maisoni S. Association of severe and fatal infections and treatment with pentostatin. Cancer Treat Rep 1986; 70: 1117-20.

8.3 Rituximab

8.3.1 Other Names

IDEC-C2B8, Chimeric anti-CD20 monoclonal antibody, Rituximab, NSC# 687451.

8.3.2 Classification

Antibody.

8.3.3 Mode of Action

Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. It binds with high affinity to CD20-positive cells, performs human effector functions *in vitro*, and depletes B cells *in vivo*. The Fab domain of rituximab binds to the CD20 antigen on B-

lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro.* The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

8.3.4 Storage And Stability

Rituximab vials are stored at refrigerated temperatures 2EC to 8EC (36E to 46EF). Protect vials from direct sunlight. Diluted drug product at a concentration of 0.5 to 4 mg/ml in polyvinylchloride or polyolefin IV bags containing normal saline or dextrose 5% can be stored for up to 24 hours at 2E to 8EC, and at room temperature for an additional 12 hours.

8.3.5 Dose Specifics

Rev. 5/06

375 mg/m^2 on weeks 1, 5, 9, 13, 17, and 21. Cycle 1 (week 1) dose varies. Please see Section 5.1 for specific doses and dosing procedures for Cycle 1.

8.3.6 Preparation

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/ml into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

8.3.7 Administration

Rituximab is administered intravenously. An in-line filter is not required. The initial rate is 50 mg/hr for the first hour. If no toxicity is seen, the rate may be escalated gradually in 50 mg/hour increments at 30-minute intervals to a maximum of 300mg/hr. If the first dose is well tolerated, the initial rate for subsequent dose is 100mg/hr, increased gradually in 100 mg/hr increments at 30-minute intervals, not to exceed 400 mg/hr. If the patient experiences fever and rigors, the antibody infusion is discontinued. The severity of the side effects should be evaluated. If the symptoms improve, the infusion is continued initially at one-half the previous rate. Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after one hour of observation, the intravenous line may be discontinued.

Oral pre-medication (two 325 mg tablets of acetaminophen and 50 to 100 mg diphenhydramine) may be administered 30 to 60 minutes prior to starting each infusion of rituximab. The patient should be treated according to the best available local practices and procedures.

The use of dexamethasone or other glucocorticoids should be discouraged.

8.3.8 Compatibility/Incompatibilities

Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

8.3.9 Availability

Commercial: Preservative-free injection 10 mg/ml, in 10 and 50 ml single-unit vials.

8.3.10 Side Effects – Please refer to package insert.

WARNINGS:

General: Rituximab is associated with hypersensitivity reactions which may respond to adjustments in the infusion rate. Hypotension, bronchospasm, and angioedema have occurred in association with rituximab infusion as part of an infusion-related symptom complex. Rituximab infusion should be interrupted for severe reactions and can be resumed at a 50% reduction in rate when symptoms have completely resolved. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids should be available for immediate use in the event of a reaction during administration.

Cardiovascular: 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 preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

Tumor Lysis Syndrome (84,85): Rituximab rapidly decreases benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop tumor lysis syndrome. Following treatment for and resolution of tumor lysis syndrome, subsequent rituximab therapy was administered in conjunction with prophylactic therapy for this syndrome in a limited number of cases.

Hepatitis B Virus: 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 4 months after the initation of rituximab and approximately one month after the last dose.

Rev. 3/05

HIV-associated lymphoma: A report in the literature described an increase in fatal infection in HIV-related lymphoma patients when Rituximab was used in combination with CHOP chemotherapy as compared to CHOP alone.

Rev. 3/05

Hematologic: In patients with Waldenstrom's macroglobulinemia, following initiation of Rituximab therapy, transcient increases in serum lgM levels have been observed which may result in hyperviscosity syndrome requiring plasmapheresis.

8.3.10.1 Incidence more frequent (> 5%)

Fever, chills, rigors, asthenia, headache, angioedema, hypotension, myalgia, dizziness, fatigue, throat irritation, abdominal pain, nausea, vomiting, leukopenia, thrombocytopenia, neutropenia, rhinitis, bronchospasm, pruritus, rash, urticaria.

8.3.10.2 Incidence less frequent (1-5%)

Flushing, arthralgia, diarrhea, anemia, cough increase, hypertension, lacrimation disorder, pain, hyperglycemia, back pain, peripheral edema, paresthesia, dyspepsia, chest pain, anorexia, anxiety, malaise, tachycardia, agitation, insomnia, sinusitis, conjunctivitis, abdominal enlargement, postural hypotension, LDH increase, hypocalcemia, hyperesthesia, respiratory disorder, shortness of breath, tumor pain, pain at injection site, bradycardia, hypertonia, tachycardia, nervousness, bronchitis and taste perversion.

8.3.10.3 Incidence rare (< 1%)

Anaphylaxis, severe infusion-related adverse events which may result in death. Tumor Lysis Syndrome: Patients with a high tumor burden or with a high number (> 50,000/mm^3) of circulating malignant cells may be at higher risk of severe infusion-related events.

When treated with Rituximab, some patients with a history of Hepatitis B may experience a reactivation of their hepatitis that may be life-threatening.

8.3.11 Nursing/Patient Implications

1. Monitor blood pressure, pulse, respiration, and temperature every 15 minutes x 4 or until stable and then hourly until the infusion is discontinued.

2. Have epinephrine for subcutaneous injections, diphenhydramine for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions available.

3. Monitor and alter infusion rates in the presence of toxicities.

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

Rituximab shows no significant effect on bone marrow reserve and no apparent increased rate of infections in heavily pretreated, relapsed lymphoma patients.

Prophylaxis for Tumor Lysis Syndrome (TLS) should be used in patients with high tumor burden, particularly with markedly elevated numbers of circulating malignant cells. Precautionary hospitalization should be made available for patients who experience severe infusional symptoms which do not resolve after discontinuation or completion of the infusion.

References

Product Information: Rituximab. IDEC Corporation, December, 1998.

Reff ME *et al.* Depletion of B cell *in vivo* by a chimeric mouse human monoclonal antibody to CD20. Blood 1994; 83:435-45.

Demidem A *et al.* Chimeric anti-CD20 antibody (IDEC-C2B8) is apoptotic and sensitizes drug resistant human B cell lymphomas and AIDS related lymphomas to the cytotoxic effect of CDDP, VP-16, and toxins. FASEB 1995; J9:A206.

Maloney DG *et al.* Phase I clinical trial using escalating single dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2D8) in patients with recurrent B-cell Lymphoma. Blood 1993; 82(Suppl 1):445a.

Maloney DG *et al.* Initial report in a phase I/II multiple dose clinical trial of IDEC-C2B8 (chimeric anti-CD20) in relapsed B-cell lymphoma. Proc Am Soc Clin Oncol 1994; 13:993.

Facts and Comparisons, March, 1998.

Date/Reviewer: February, 1999/Darryl Grendahl, R.Ph. (507) 284-2701

8.4 CAMPATH-1H

8.4.1 Other Names

CAMPATH-1H monoclonal antibody, Alemtuzumab.

8.4.2 Classification

CAMPATH-1H is a humanized antilymphocyte monoclonal antibody engineered by grafting the rodent hypervariable complementarity determining regions into a human immunoglobulin variable framework region. CAMPATH-1H is expressed in recombinant CHO cells. It is directed against the CD52 surface antigen expressed on lymphocytes at nearly all stages of differentiation.

8.4.3 Mode of Action

The CAMPATH -1 antigen in humans is predominantly expressed on peripheral blood lymphocytes, monocytes, and macrophages. CAMPATH -1H causes the lysis of lymphocytes by fixing to CD52, a highly expressed, non-modulating antigen on the surface of lymphocytes. CAMPATH -1H antibodies elicit cell lysis through effector mechanisms including opsonization, complement (C') fixation and antibody dependent cell-mediated cytotoxicity (ADCC) as well as broad reactivity with normal and malignant human lymphoid cells.

8.4.4 Storage and Stability

Intact ampules are to be stored at refrigerated temperature and protected from direct sunlight.

8.4.5 Dose Specifics

30 mg sc tiw for 4 weeks (Arm B) or 30 mg sc tiw for 18 weeks (Arm C) depending on patient randomization.

8.4.6 Preparation

Not applicable.

8.4.7 Route of Administration

For subcutaneous injection, CAMPATH-1H should be withdrawn into the syringe using sterile, low protein binding, non-fiber releasing 5-micron filter. The appropriate dose of CAMPATH-1H may be administered undiluted in up to three divided doses with no more than 1 mL per injection.

8.4.8 Compatibilities

No information available.

8.4.9 Availability

Commercial: CAMPATH-1H is supplied in glass ampoules containing 30 mg of antibody in 3 ml of sterile phosphate buffered saline (concentration of 10 mg/ml) with 0.05 mm EDTA. Tween 80 is added to a concentration of 0.01%. Ampoules are supplied in boxes of 10 ampoules/box. Ampoules must be used on a per patient, single use basis.

8.4.10 Side Effects – Please refer to package insert.

Rev. 5/10

Adverse Events

Please refer to CAEPR Section 5.3.9.

Contraindications

CAMPATH-1H is contraindicated in those patients who are hypersensitive to this drug or its components. CAMPATH-1H is contraindicated in patients who have serious infections. CAMPATH-1H is contraindicated during pregnancy and lactation.

Incidence more frequent (> 5%)

Rigors, fever, fatigue, skin reactions (erythema/edema, pruritis, and slight pain), neutropenia, and CMV reactivation.

CAMPATH-1H is a potent lymphocyte-depleting agent. Neutropenia and thrombocytopenia emerge on treatment in approximately 10-20% of patients.

Incidence rare (< 1%)

Overdoses of up to 240 mg CAMPATH-1H have been given without any significant additional toxicity being observed. There is no known

specific antidote for CAMPATH-1H overdose. Treatment consists of drug discontinuation and supportive therapy.

Rev. 5/10

Rev. 5/10

8.4.11 Nursing/Patient Implications

Patients should be premedicated with 50 mg diphenhydramine and 650 mg of acetaminophen 30 minutes prior to the first CAMPATH-1H injection. The premedication is to be given with the first dose and thereafter if clinically indicated.

Careful hematologic and non-hematologic (including infection) monitoring is indicated for patients receiving CAMPATH-1H.

Infections resulting from CAMPATH-1H induced immunosuppression are the major type of adverse event occurring outside the CAMPATH-1H administration period. The most commonly reported infections are mucocutaneous herpes simplex, CMV, and candidiasis. If a patient develops a serious infection while receiving CAMPATH-1H, therapy should not be administered until complete resolution of the infection. CAMPATH-1H may then be reinstituted at the previous dose.

CAMPATH-1H is contraindicated in those patients who are hypersensitive to this drug or its components. CAMPATH-1H is contraindicated in patients who have serious infections. CAMPATH-1H is contraindicated during pregnancy and lactation.

8.4.12 References

Dyer MVS, Hale G, Hayhoe FGJ, Waldmann H. Effects of CAMPATH-1 Antibodies in vivo in patients with lymphoid malignancies: influence of antibody isotype. Blood 1989 73:1431-9.

Personal Communication. Ilex Oncology Services, Inc. December 1998.

9. Statistical Considerations

9.1 Primary Endpoints

The primary endpoints of this Phase II trial of PCR followed by CAMPATH-1H in previously treated B-CLL patients are i) to determine the response (CR, nPR, PR) rate of PCR in all patients treated with PCR, and ii) to determine the rate of molecular complete remission (MCR) after the treatment of CAMPATH-1H in patients who achieve a CR or nPR.

Patients who achieve a CR or nPR, minimal residual disease (MRD) will be assessed using both flow cytometry and real-time allele specific oligonucleotide polymerase chain reaction (RT-PCR), and response will be further categorized as clinical CR or nPR (CCR) with flow positive, CCR with flow negative but RT-PCR positive, or CCR with flow negative and RT-PCR negative (MCR).

Response to PCR will be assessed prior to the administration of CAMPATH-1H, and MCR will be assessed post PCR administration, post CAMPATH-1H administration, and at 3 months post CAMPATH-1H. For patients who continue in CR or nPR, their MRD status will be monitored every three months.

The study is a two-stage design for the response endpoint. PCR will be considered promising in this patient population if a true response rate of 50% or greater and not worthy if less than a 30% response rate. A total of 100 eligible patients will be entered in this study: 26 in the first stage and 74 in the second stage. At the end of the first stage of accrual, data will be reviewed to determine if the study should be terminated due to lack of activity of the proposed regimen. If 9 or fewer patients achieve a response in the first stage, the study will be terminated. If 10 or more patients achieve a response, the study will proceed to the second stage, accruing an additional 74 patients to yield a total of 100. If 35 or more responses are observed after the second stage, then PCR will be considered promising. Conversely, if less than 35 patients respond, then PCR will not be recommended for further investigation.

With this design, the probability of terminating the study after 26 patients is 0.77 if the true but unknown response rate is 30%, but 0.08 if the true but unknown response rate is 50%. The probability of concluding the regimen effective is 0.92 if the true response rate is 50% and 0.08 if the true response rate is 30%.

Table 1 below summarizes the operating characteristics of two-stage design.

Table 1

	True Response Rate		
	30%	40%	50%
Prob. stopping early (≤ 10 responses in 26 eligible pts)	0.77	0.36	0.08
Prob. concluding effective (>= 35 responses in 100 eligible pts)	0.08	0.60	0.92

To investigate whether CAMPATH-1H eliminates minimal residual disease (MRD) in CR or nPR, MRD will be assessed by both flow cytometry and RT-PCR as described above. The proportion of pre-to-post treatment improvement in response will be estimated as (total number of samples with a MCR at 3 months post CAMPATH-1H) divided by (total number of samples of any changes in response), and whether this proportion is different from the random chance improvement 0.5 will be tested using McNemar's test. Assuming the study proceeds to the second stage and at least 30 eligible patients will achieve a CR or nPR after the PCR treatment, Figure 1 shows power for detecting the true pre-to-post treatment improvement to MCR given any change in response.

In the study of previously untreated B-CLL patients at Mayo clinic, about 50% of patients in the CR or nPR group presented a MCR after PCR and prior to CAMPATH-1H. Based on this information, we assume that about 30% of previously treated B-CLL patients in the CR or nPR group will have a MCR prior to CAMPATH-1H, and an additional 30% or more patients will achieve a MCR at 3 months post CAMPATH-1H. For example, if there are 9 MCRs prior to CAMPATH-1H, the 9 additional patients achieve a MCR at 3 months post CAMPATH-1H, and no patient experiences his/her response worsened, there will be approximately 97% power to detect this pre-to-post treatment improvement in response. If, however, only 8 out of the 9 additional patients with any response change achieve a MCR at 3 months post CAMPATH-1H, there will be approximately 73% power. Alternatively, if there are 9 MCRs prior to CAMPATH-1H, 12 experience any change in response, and 11 out of those 12 patients achieve a MCR at 3 months post CAMPATH-1H, there will be approximately 91% power. This power calculation is based on McNemar's test at the one-sided 0.05 significance level, using PROC IML in SAS with 10,000 simulations.

When data are available, whether MRD status is associated with relapse and whether MCR suggests any survival implication will be explored using an Andersen-Gill type survival analysis to accommodate the time-varying covariate of response.

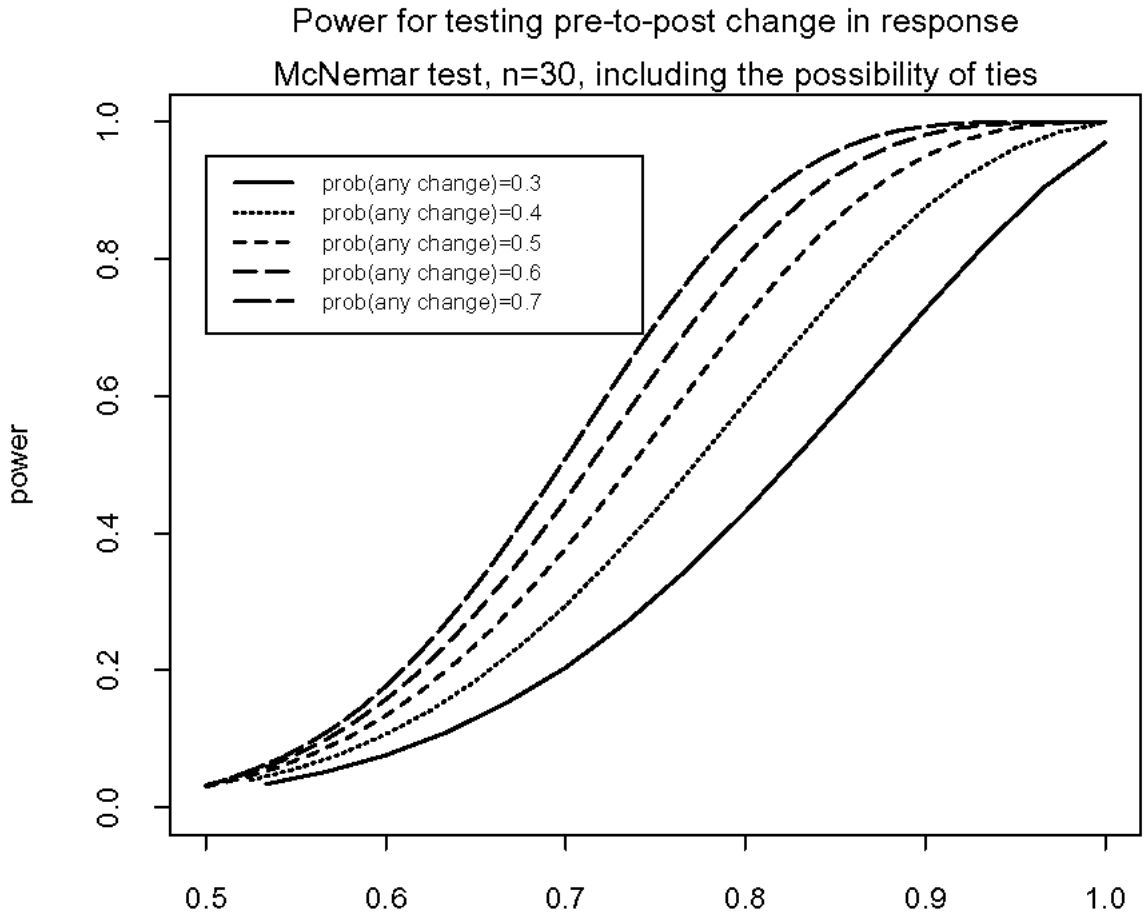

Figure 1

9.2 Accrual

Accounting for 10% ineligibility, the overall accrual goal will be 110 patients. The previous ECOG study in this patient population (E4996) accrued poorly. However, the proposed chemoimmunotherapy, PCR+CAMPATH-1H, is very different from the regimen used in E4996 (VAD+PSC) and appears promising in literature. Mayo clinic, an ECOG-ACRIN member institution, sees 4-5 previously treated B-CLL patients per month. Putting this together, we anticipate that the accrual rate will be approximately 60-70 patients per year and the accrual will be completed in 1.5 years.

Although the study is expected to encounter no accrual problem, the feasibility of achieving the accrual goal will be monitored closely. If accrual rate is slower (30 or fewer patients per year) than anticipated, the study will be reviewed for early termination.

9.3 Early Stopping for Excessive Toxicity

Since this regimen has not been examined in a cooperative setting, all toxicities will be monitored closely and reported using ECOG-ACRIN's standard AE mechanism.

The tolerability of the proposed regimen will be initially tested in the first 30 patients for PCR and in the first 50 patients for CAMPATH-1H separately. Since there will be an 8 week treatment-free period between PCR and CAMPATH-1H treatment, we assume that PCR related toxicities and CAMPATH-1H related toxicities will be independent.

We will consider PCR or CAMPATH-1H tolerable if 30% or less grade 3 or higher regimen related toxicity and intolerable if 50% or higher. If, in the first 30 patients treated with PCR, we observe 13 or more patients with grade 3 or higher PCR related toxicity, the study will be terminated to further accrual. With this design, the probability of terminating the study early is 0.08 if the true but unknown rate of grade 3 or higher toxicity is 30%, and the probability of terminating the study early is 0.82 if the true but unknown rate of grade 3 or higher toxicity is 50%.

Toxicity profile for CAMPATH-1H will be evaluated for CR or nPR and for PR or less response separately since CAMPATH-1H will be given for 4 weeks for CR or nPR and for 18 weeks for PR or less response, and the toxicity profile for these two subpopulations may be different.

In the first 50 patients, we assume about 15 patients will achieve a CR or nPR and about 35 patients will have a PR or less response.

Of these 15 patients with CR or nPR, if we observe 8 or more patients with grade 3 or higher CAMPATH-1H related toxicity, the study will be terminated to further accrual. With this design, the probability of terminating the study early is 0.05 if the true but unknown rate of grade 3 or higher toxicity is 30%, and the probability of terminating the study early is 0.5 if the true but unknown rate of grade 3 or higher toxicity is 50%.

Of the 35 patients with PR or less response, if we observe 16 or more patients with grade 3 or higher CAMPATH-1H related toxicity, the study will be terminated to further accrual. With this design, the probability of terminating the study early is 0.04 if the true but unknown rate of grade 3 or higher toxicity is 30%, and the probability of terminating the study early is 0.75 if the true but unknown rate of grade 3 or higher toxicity is 50%.

9.4 Secondary Endpoints

Overall survival (OS) and progression-free survival (PFS) will be assessed for all patients and by response category. OS is defined as the time from registration until death from any cause. PFS is defined as the time from registration until induction failure, institution of non-protocol therapy, relapse or death from any cause in the absence of relapse. OS and PFS will be calculated using the Kaplan-Meier method, and confidence limits will be calculated using the Greenwood formula.

For about 70 patients who do not achieve CR or nPR, response will be re-assessed every three months to examine whether CAMPATH-1H improves their response and the rate of conversion to a higher response category (call it "improvement") at 1-year from study entry will be estimated. With 70 eligible

patients, if we observe 12 or more patients with improvement, CAMPATH-1H will be considered promising in this patient population. Deaths without improvement of response prior to re-assessment will be regarded as no improvement. With this design, the probability of concluding CAMPATH-1H promising is 0.96 if the true but unknown improvement rate is 25% and 0.04 if the true but unknown improvement rate is 10%. This decision rule is calculated using an exact binomial distribution.

9.5 Laboratory Endpoints

The goal of this laboratory study is to investigate new biologic parameters with utility as risk stratification parameters (FISH, CD38 expression, IgVH mutational status and angiogenesis profiles). Statistical plans for all laboratory correlative studies are based on the assumption that the study will proceed to the second stage and complete with 100 eligible patients.

9.5.1 To investigate the association between angiogenesis profiles and clinical outcome, serum levels of VEGF and bFGF, secreted levels of both pro- and anti-angiogenic factors from purified CLL B cells and levels of bone marrow angiogenesis will be assessed at study entry and after treatment. Descriptive statistics (mean, STD, median, range, frequency) will be reported for each pro- (e.g., bFGF, VEGF) or anti-angiogenic (e.g., Thrombospondin-1,) factor. In the report of Kay et al. (100), the mean VEGF levels were 6.6 pg/ml (+/- 3.2) for high-risk B-CLL patients (n=11, Rai stage 3-4) and 2.4 pg/ml (+/- 0.7) for low-risk B-CLL patients (n=18, Rai stage 0), and the mean bFGF levels were 337.9 pg/ml (+/- 254.5) for high-risk patients and 72.1 pg/ml (+/- 25.6) for low-risk patients. However, there seem to be little difference in the median levels of these angiogenic factors between two patient cohorts (see Figure 2 in Kay et al, 2000). On the contrary, in the unpublished manuscript of Kay et al. (Angiogenic Status of Blood B Cells in B-CLL), the mean VEGF levels were 3.9 (+/- 3.8) for Rai stage 3-4 (previously treated patients), 3.2 (+/- 3.4) for Rai stage 1-2, and 12.4 pg/ml (+/- 14.8) for Rai stage 0 (previously untreated patients), and the mean bFGF levels were 7.5 pg/ml (+/- 2.6) for Rai stage 3-4, 10.4 pg/ml (+/- 7.2) for Rai stage 1-2, and 11.6 pg/ml (+/- 3.9) for Rai stage 0.

Having this information in mind, we will assess each pro- or anti-angiogenic factor separately before and after the treatment and investigate in a cooperative setting whether the angiogenic factors are associated with clinical outcome and whether the treatment affects the level of each angiogenic factor. Assuming about 30 patients will be in the CR or nPR group and 70 in the PR or less response group, there will be approximately 84% power if the mean difference in VEGF level at baseline between these two groups is 2 pg/ml with standard deviation of the difference 3, and 92% power if the difference is 3 pg/ml with standard deviation of the difference 4. This power calculation is based on the asymptotic power of the Wilcoxon-Rank-Sum test for normal treatment difference alternative at two-sided significance level of 0.05.

The pre-to-post treatment difference of each angiogenic factor will be evaluated in each response group. If the mean VEGF levels are 6 pg/ml at baseline and 4 pg/ml post treatment for patients who achieve a CR or nPR, there will be approximately 93% power to detect this pre-to-post difference in VEGF level if the standard deviation of the difference is 3 and approximately 83% power if the standard deviation of the difference is 3.5. This power calculation is based on the Wilcoxon signed-rank test at the two-sided 0.05 significance level, using PROC IML in SAS with 10,000 simulations.

When data are available, correlation analysis will be performed to explore potential relationship between anti- and pro-angiogenic factors, the association between angiogenesis profiles and clinical outcome will be summarized descriptively, and logistic regression analysis and a survival model will be performed to assess the association further.

9.5.2 The IgVH gene mutation status will be assessed at study entry and the relationship between IgVH mutation status and clinical outcome will be investigated. It is anticipated that approximately 40% of patients will have IgVH gene mutation (99) at study entry and these patients will show better prognosis. With 100 eligible patients, there will be approximately 85% power for detecting a 32% difference in response rate if response rates are 69% for patients with mutation and 37% for patients without mutation, and 79% power if response rates are 68% and 38%, respectively. This power calculation is based on Fisher's exact test at a two-sided significance level of 0.05 and assumes 50% overall response rate. When data are available, whether IgVH gene mutation status is associated with CD38 expression level will be examined using a 2x2 table analysis and a Wilcoxon-Rank-Sum test and whether IgVH gene mutation status and CD38 expression level are prognostic factors will be examined using a survival model, such as proportional hazards model or cure rate model.

To explore whether CD38 expression level is an independent prognostic marker for B-CLL, CD38 expression will be measured at study entry. The expression level will be analyzed on a continuous scale and will be dichotomized, i.e., CD38+ if CD38 > =30% and CD38- if CD38 < 30% (66). Based on the study of Dewald, et al. (99), we assume that about 40% of patients will be CD38+ and 60% will be CD38-. If response rates for these two groups are 31% and 63%, respectively, there will be approximately 85% power to detect this difference and 79% power if 32% and 62% response rates, respectively. This power calculation is based on Fisher's exact test at a two-sided significance level of 0.05 and assumes 50% overall response rate. Progression free and overall survival was also reported from small clinical trials of previously untreated B CLL patients (60,86). Conservatively extrapolating their report to previously treated patients, there will be approximately 80% lower if the median progression free survival time is 23 months in the CD38- group and 12 months in the CD38+ group, assuming 60 and 40 patients in the

CD38- and CD38+ group, respectively. This power calculation is based on the log-rank test at the two-sided significance level of 0.05 and assumes exponential survival distribution.

9.5.3 To investigate whether genetic defects seen in B-CLL patients are associated with clinical outcome, the percentage of abnormal nuclei with chromosome anomalies, the frequency of anomalies of chromosomes 6-, 11-, 12-, 13-, 14- and 17 will be estimated among responders and non-responders separately. As described in Dewald, et al.(74) a hierarchical risk model of FISH anomalies in B-CLL will be used to order anomalies from the most aggressive to the least aggressive, and the association between this ordered categorical variable and clinical response will be examined using the exact Wilcoxon test. According to Dewald, et al., about 23% of patients with progressive disease falls into a high risk FISH category. Thus, if 23 out of 100 eligible patients fall into the high-risk category and the clinical response rates are 23% in this high-risk category and 58% in the intermediate or low-risk group, there will be approximately 81% power to detect this difference. This power calculation is based on Fisher's exact test at a two-sided significance level of 0.05 and assumes 50% overall response rate. Kappa analysis will also be performed to assess the agreement between two technologists who analyze the interphase nuclei.

9.5.4 To study whether patients with B-CLL present defects in the T cell repertoire (TCR) at study entry and to investigate the impact of the proposed chemoimmunotherapy on TCR, peripheral blood samples will be collected at pre and post treatment (after PCR and after Campath-1H for responders and after Campath-1Hfor non-responders) and $CD3^+$ blood lymphocytes will be analyzed by flow-cytometric Vβ and Vα repertoire analysis. The flow-cytometric Vβ and Vα analysis uses monoclonal antibodies directed against 18 specific Vβ and Vα chains in two color flow with either CD4 or CD8 reactive monoclonal antibodies, and it covers 70% of the human T cell repertoire. In the report of a phase 2 trial for previously untreated CLL patients at Mayo clinic, dramatic elevations in blood T cell subsets for responding patients were observed and the percent CD3+ was from 60-86%. Of 11 patients studied in their analysis, the major expansions (20-70%) occurred at Vβ3, 7.1, 9, and 17. Based on this information, if there is a 20% difference in a specific Vβ subfamily or in the percent CD3+ between responders (CR+ nPR) and non-responders after treatment, there will be a 92% power to detect this difference if its standard deviation is 15%. This power calculation assumes a 30% CR+ nPR rate and is based on Wilcoxon-Rank-Sum test for normal group difference alternative at the two-sided significance level of 0.05.

9.6 Gender and Ethnicity

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	3	6	9
Not Hispanic or Latino	30	71	101
Ethnic Category: Total of all subjects	33	77	110
Racial Category			
American Indian or Alaskan Native	1	2	3
Asian	1	2	3
Black or African American	4	8	12
Native Hawaiian or other Pacific Islander	1	1	2
White	26	64	90
Racial Category: Total of all subjects	33	77	110

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.7 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.3.

Rev. 5/06

10. [Section 10 Deleted in Addendum #9, 5/06]

11. Correlative Studies

NOTE: An informed consent MUST be signed prior to the submission of any material for any correlative study, including mandatory diagnostic reviews. Samples for optional correlative studies should be submitted only from patients who have given written consent for the use of their samples for these purposes.

NOTE: Three sample submissions are described for these studies. The collection and submission requirements outlined in Section 11.1 are mandatory. Samples described in Sections 11.2, and 11.3 are to be submitted from patients participating in the optional studies.

NOTE: An E2903 Material Submission Form #1847 must be submitted with each submission. All samples, sample treatments, and collection time points are to be indicated on the form(s). The original E2903 Material Submission Form #1847 should accompany the samples to the central laboratory(ies). Please forward a copy of the original form to the ECOG-ACRIN Operations Office - Boston (Attn: Translational Sciences) at the same time it is sent to the central laboratory.

Rev. 1/09

11.1 Immunophenotype and Molecular Genetics

NOTE: Samples are required for diagnostic review.

Immunophenotyping has become an essential part of the diagnostic work-up of all leukemia patients. In fact, the diagnosis of leukemia without immunophenotypic characterization is no longer acceptable. ECOG-ACRIN has, therefore, developed a model system for antigenic data collection that requests specimens from all patients entered on ECOG-ACRIN leukemia treatment trials be studied by ECOG-ACRIN's Immunophenotyping Reference Laboratory. In addition to establishing the leukemia subtype, this centralized testing and data collection has allowed that research questions of clinical relevance to be applied to a growing database (e.g., definition of prognostically significant antigen expression levels to eventually yield specific treatment subcategories). Depending on the study protocol and tissue availability, anti-coagulated (heparin, EDTA, ACD) peripheral blood or bone marrow or both are to be submitted to ECOG-ACRIN's Immunophenotyping Reference Laboratory.

In addition to the study of abnormal hematopoietic cells, the focus of research on circulating serum factors in patients with leukemia or myelodysplasia has increased. Two tubes of coagulated peripheral blood (red top tubes) are requested for future research studies that may aim at identifying pathogenetic, diagnostic, or prognostic factors associated with leukemia or myelodysplasia.

Serum and cells from peripheral blood or bone marrow from patients entered on studies of hematologic malignancies are stored in ECOG-ACRIN's Leukemia Tissue Bank for future laboratory studies. The bank provides the scientific community a source of leukemia specimens that are collected, processed, and maintained following quality control and quality assurance guidelines. The bank will accommodate requests from investigators within and outside ECOG-ACRIN in a timely and efficient manner, with respect to tissue type, tissue preparation, and most importantly, biologic characteristics of specimens.

11.1.1 Sample Submission Schedule

Samples are to be submitted at the following time points:

- Pretreatment

Samples are to be shipped on the day they are drawn. If this is not possible, call the Immunophenotyping Reference Laboratory.

If you have questions, contact the Immunophenotyping Reference Laboratory (718) 920-9992.

Rev. 1/09

NOTE: Dr. Paietta's institutional regulations require that she receive a copy of the patient consent and a copy of the HIPAA authorization form along with samples.

11.1.2 Sample Preparation Guidelines

11.1.2.1 The following MUST be submitted:

1. Heparinized peripheral blood (2 green top tubes, 10-20 mL)

   NOTE: Submission of pathologic materials for diagnostic review is mandatory in order for the patient to be considered evaluable. Failure to submit pathologic materials will render the case unevaluable.

An E2903 Material Submission Form (#1847) must be submitted with each shipment, listing all sample types, collection times, patient's disease, and patient's status at time of collection (e.g., PR, CR, relapse).

11.1.2.2 The following should be submitted to be banked for use in future studies:

One red top serum tube of peripheral blood (10mL)

NOTE: Submission of banking samples is optional. If samples designated for banking only are not submitted, please note the reason in the Comments section of the Material Submission Form.

11.1.3 Shipping Procedures

The Immunophenotyping Reference Laboratory **must** be notified by telephone, 24 hours prior to the arrival of a sample. **Fax is not acceptable**.

Telephone: (718) 920-9992 Beeper (off hours): (917) 729-7231

Heparinized samples and serum must be sent fresh (on the day of collection) **on wet/cool packs** (do not freeze) by overnight courier (preferably Federal Express) to arrive within 24 hours to:

Rev. 1/09

Elisabeth Paietta, Ph.D.
Montefiore Northern Division
Cancer Center
600 East 233rd Street
Bronx, NY 10466
Tel: (718) 920-9992

The laboratory is open to receive shipments Monday through Saturday. Shipments on Fridays for Saturday delivery must have "Saturday Delivery" marked on the overnight courier slip.

11.1.4 Banking

The residuals and/or derivatives of samples collected for this study will be retained at the Immunophenotyping Reference Laboratory for possible use in ECOG-ACRIN approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.2 FISH Studies (99)

Chromosomal anomalies detected by interphase FISH are among the most important factors predicting survival in CLL. We believe that these FISH detectable chromosome anomalies are associated with other biological features in CLL that also have prognostic value such as antigen expression on leukemic B-lymphocytes. The interphase FISH results will be used to classify each patient to a FISH risk category for CLL based on 13q- and normal as favorable, and 6q-, 11q- and/or 17 as unfavorable. We will establish the percentage of abnormal nuclei with chromosome anomalies before and after therapy to assess response to therapy. The results will help assess the efficacy of the treatments under evaluation in this clinical trial. At the end of the clinical trial, the results of FISH will be compared with other laboratory and clinical information in an effort to learn more about the biology of CLL. Results will be correlated with clinical assessments, outcome, gene expression profiles and other biological parameters.

CLL B-cell FISH Analysis: Analysis by a CLL FISH panel will be done in order to determine if the recurring genetic defects seen in B-CLL patients entered onto the companion clinical trial are predictive of clinical status and outcome. We will perform FISH studies on blood cells isolated from our patients with CLL. The "panel FISH test" we have developed is used to detect common chromosome abnormalities associated with B-cell neoplasms including B-CLL (99,105). Thus, the FISH panel is designed to detect 1) 11;14 translocations that involve cyclin D1 (11q13) and IgH (14q32) loci; 2) deletions of MYB (6q21), ATM (11q23), D13S319 (13q14) and P53 (17p13.3); and 3) trisomy 12. The 11;14 probe is included in this panel to help assure that our patients represent well-documented cases of B-CLL and not Mantle cell lymphoma. For each blood cell specimen, we will score the cells in a blind fashion to avoid knowing whether the specimen is from a patient, normal control or pre- or post-therapy specimen. For each specimen and each probe, two independent technologists will each analyze 100

interphase nuclei that meet the scoring criteria; thus, a total of 200 nuclei will be scored for each specimen. We have already determined the normal ranges for these probes from data from the normal controls (99). The results of the panel FISH test will be correlated with treatment and all other biological and clinical aspects of patients enrolled in this study (see Section 9.0).

Rev. 1/09

These analyses will be performed by the ECOG-ACRIN Cytogenetics Laboratory under the direction of Dr. Rhett Ketterling.

11.2.1 Sample Submission Schedule

Peripheral blood should be collected and submitted at:

- baseline (prior to therapy)
- after PCR therapy,
- after CAMPATH-1H, or at discontinuation of protocol treatment.

Samples are to be submitted the day of collection. Questions concerning sample preparation and sample submission should be directed to Mr. Gary Hicks, telephone # (507) 284-2950.

11.2.2 Sample Preparation Guidelines

Peripheral blood (5 ml) should be collected in sodium heparin and sent fresh (within 1 to 5 hours of drawing) on wet ice (do not freeze). Samples should be labeled with protocol number, patient sequence number, patient's initials and date specimen drawn.

11.2.3 Shipment Procedures

The E2903 Material Submission Form #1847 must be submitted with each sample to ensure proper identification and processing of the specimen. Send blood specimens refrigerated (do not freeze) by overnight courier to arrive within 24 hours to:

Mr. Gary Hicks
Mayo Clinic
Cytogenetics Laboratory
970 Hilton Building
200 Second Street SW
Rochester, MN 55905
Ph: (507) 284-2950

The Cytogenetics Laboratory will be open to receive shipments Monday-Saturday. Shipments on Friday for Saturday delivery must have "Saturday Delivery" marked on the overnight courier slip. Notify Cytogenetics Laboratory prior to shipping samples and to obtain the FedEx account number.

11.2.4 Banking

The residuals and/or derivatives of samples collected for this study will be retained at the Cytogenetics Reference Laboratory at Mayo for possible use in ECOG-ACRIN approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.3 Additional Laboratory Studies

Rev. 1/09

These studies will be done on serum, malignant cells from the blood of B-CLL patients entering this protocol.

The correlative studies will be performed under the direction of Dr. Neil Kay at the Mayo Clinic in Rochester, Minnesota.

11.3.1 The studies to be performed:

11.3.1.1 Minimal residual disease assessment by ASO-PCR

Blood samples collected from patients attaining CR or nPR will be assessed for MRD by allele specific oligonucleotide-polymerase chain reaction (ASO-PCR) at time of assessment of response, post-CAMPATH-1H administration, and every 6 months after CAMPATH-1H. The sample collection timing for CR or nPR in this study will be different from PR or less response since the duration of CAMPATH-1H treatment is different between CR and nPR and PR or less response.

11.3.1.2 Ig VH mutational analysis

The VH gene mutation status will be assessed at baseline.

11.3.1.3 Angiogenesis studies

Secretion levels of pro- and anti-angiogenic factors (bFGF, VEGF, TSP1, of CLL B-cell clones will be measured at study entry, at time of assessment of response, post-CAMPATH-1H administration, and every 6 months after CAMPATH-1H. The sample collection timing for CR or nPR in this study will be different from PR or less response since the duration of CAMPATH-1H treatment is different between CR or nPR and PR or less response.

11.3.1.4 CD38+ expression level

CD38+ expression level will be measured at study entry.

11.3.1.5 T cell repertoire

T cell repertoire will be studied using flow cytometry and methodology. These will be measured at study entry, at time of assessment of response, post-CAMPATH-1H administration, and every 6 months after CAMPATH-1H.

11.3.1.6 Sample Submission Schedule

Rev. 1/09

Peripheral blood and marrow samples are requested at the intervals indicated below.

Rev. 1/09

NOTE: For patients who consent to the laboratory studies, please submit ALL sequential blood specimens at ALL time points.

Sample Type	Baseline	After PCR	After CAMPATH-1H or Discontinuation of Protocol Treatment	Q 6 months[1]	Time of Response assessment
Peripheral Blood (green top)	10 tubes	5 tubes	5 tubes	5 tubes	
Peripheral Blood (red top)	1 tube	1 tube	1 tube	1 tube	
Marrow Slides/ Tissue	X	X	X		X[2]

1. Samples are requested at baseline, after completion of PCR, after competion of Campath, and every six months following therapy for 5 years from start of therapy.

Rev. 1/09

2. Bone marrow block or 8-10 unstained, positively charged slides are requested. Samples should be submitted at any time a BM is performed to assess response.

Peripheral blood is to be shipped the day of collection. Bone marrow blocks or slides should be submitted within one month of collection. Follow the packaging and shipping guidelines in Appendix VIII.

Baseline kits are to be ordered at least one week in advance.

Rev. 7/07

11.3.1.7 Correlative Studies Kit Instructions

Rev. 1/09

1. Kits will be supplied through Dr. Neil Kay's laboratory. Participating institutions may obtain kits by contacting Charla Secreto at (507) 284-3805.
2. The appropriate type and number of collection tubes will be contained within each specimen collection kit, along with the Federal Express Mail Form.

11.3.2 Sample Preparation Guidelines

All specimens are to be clearly labeled with the protocol number E2903, the patient's initials, and sequence number, hospital number and date of collection. The Patient Information Form (Appendix IX) should be completed at the time of collection of the specimens.

11.3.2.1 Peripheral Blood

1. Baseline Samples:
   - Ten (10) 10 mL green top tubes
   - One (1) 10mL red top tube
2. All other time points:
   - Five (5) 10mL green top tubes
   - One (1) 10 mL red top tube

11.3.2.2 Bone Marrow

Rev. 1/09

Submit a bone marrow block or 8-10 unstained, positively charged slides. This sample should be shipped separately.

11.3.3 Shipping Procedures

Rev. 1/09

Peripheral blood specimens should be mailed the day they are obtained and shipped overnight to arrive during normal working hours. Bone marrow blocks and slides, if shipped separately, are to be shipped within one month of collection (please include a cold pack during warm weather).

Follow the packaging and shipping guidelines listed in Appendix VIII. If samples are sent late in the week and will arrive on the weekend, please note "Saturday Delivery" on the Federal Express form.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

Rev. 7/07

Please call Charla Secreto at (507) 284-3805 when samples are being mailed.

Rev. 1/09

Using the mailer provided in the kit, ship the samples at room temperature by overnight Federal Express to:

Rev. 1/09

Charla Secreto
Mayo Clinic
613 Stabile
200 First Street, SW
Rochester, MN 55905

The E2903 Material Submission Form (#1847) must be submitted with each sample submission, listing all sample types, collection times, and patient's status at the time of collection (e.g., baseline, 6 months, etc.).

11.3.4 Banking

The residuals and/or derivatives of samples collected for the correlative studies described in Section 11.3 will be forwarded and retained at the Leukemia Translational Studies Laboratory for possible use in ECOG-ACRIN approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.4 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used on the above mentioned laboratory correlative study(ies) will be submitted to the ECOG-ACRIN Operations Office - Boston on a quarterly basis. Inventories will be submitted electronically or by diskette by any laboratory holding and/or using any specimens associated with this study. Electronic submissions should be submitted to ecog.labdata@jimmy.harvard.edu. All other correspondence should

Rev. 1/09

be addressed to the attention of the Translational Science Team.

11.5 Lab Data Transfer Guidelines

The data collected on the above mentioned correlative study(ies) will be submitted to the ECOG-ACRIN Operations Office - Boston by the central laboratory(ies) on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30 and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates. Electronic submissions should be submitted to ecog.labdata@jimmy.harvard.edu. All other

Rev. 1/09

correspondence should be addressed to the attention of the Translational Science Team.

12. Records To Be Kept

Please refer to the E2903 Forms Packet for the forms submission schedule and copies of all forms. The E2903 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

13. Patient Consent And Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Rev. 7/07

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Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #14]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #14 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Rev. 5/06

[Appendix II Deleted in Addendum #9, 5/06]

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Appendix III

Neupogen® Information

Reimbursement Support for Neupogen®

Amgen, the manufacturer of Neupogen® (Filgrastim), has agreed to provide Neupogen® reimbursement assistance through its Amgen Reimbursement Hotline for E2903 Phase II Randomized Trial of Pentostatin, Cyclophosphamide, Rituximab and CAMPATH-1H for Previously Treated Chronic Lymphocytic Leukemia.

As indicated in Section 5.1.4.4 of the protocol's treatment plan, Neupogen® should be administered at 5 ug/kg/d SC at least 48 hours following the completion of chemotherapy (day 3) and continued through day 12 or until post-nadir ANC > 10,000/mm^3. Filgrastim must be stopped 48 hours prior to next cycle of chemotherapy regardless of the ANC. The recommended day to start G-CSF is Day 3. These uses of Neupogen® are within approved FDA labeling. However, it is anticipated that some insurers may be reluctant or unable to cover patients treated with Neupogen® in this trial. Amgen's Reimbursement Hotline is prepared to assist in providing up-to-date claims advice for these situations. The Hotline's services have been expanded specifically for this clinical trial and include:

1. **Reimbursement Support**: The Hotline provides assistance relating to claims filing and appeals, and identification of alternative sources of payment (secondary insurer, state programs, and charity programs).
2. **Claims Support**: The Hotline provides claims appeal support at several different levels, including investigating claims denials, preparing the claims appeal, assisting with letters of medical necessity, and providing necessary supporting literature.

The schema on the following page outlines the options should reimbursement assistance be required.

SHOULD THE HOTLINE VERIFY THE PATIENT HAS NO INSURANCE OR NEUPOGEN® IS NOT COVERED, THEY WILL COORDINATE WITH AMGEN THE REPLACEMENT OF PRODUCT USED BUT NOT REIMBURSED BY THE INSURER.

NEUPOGEN® REIMBURSEMENT HOTLINE:

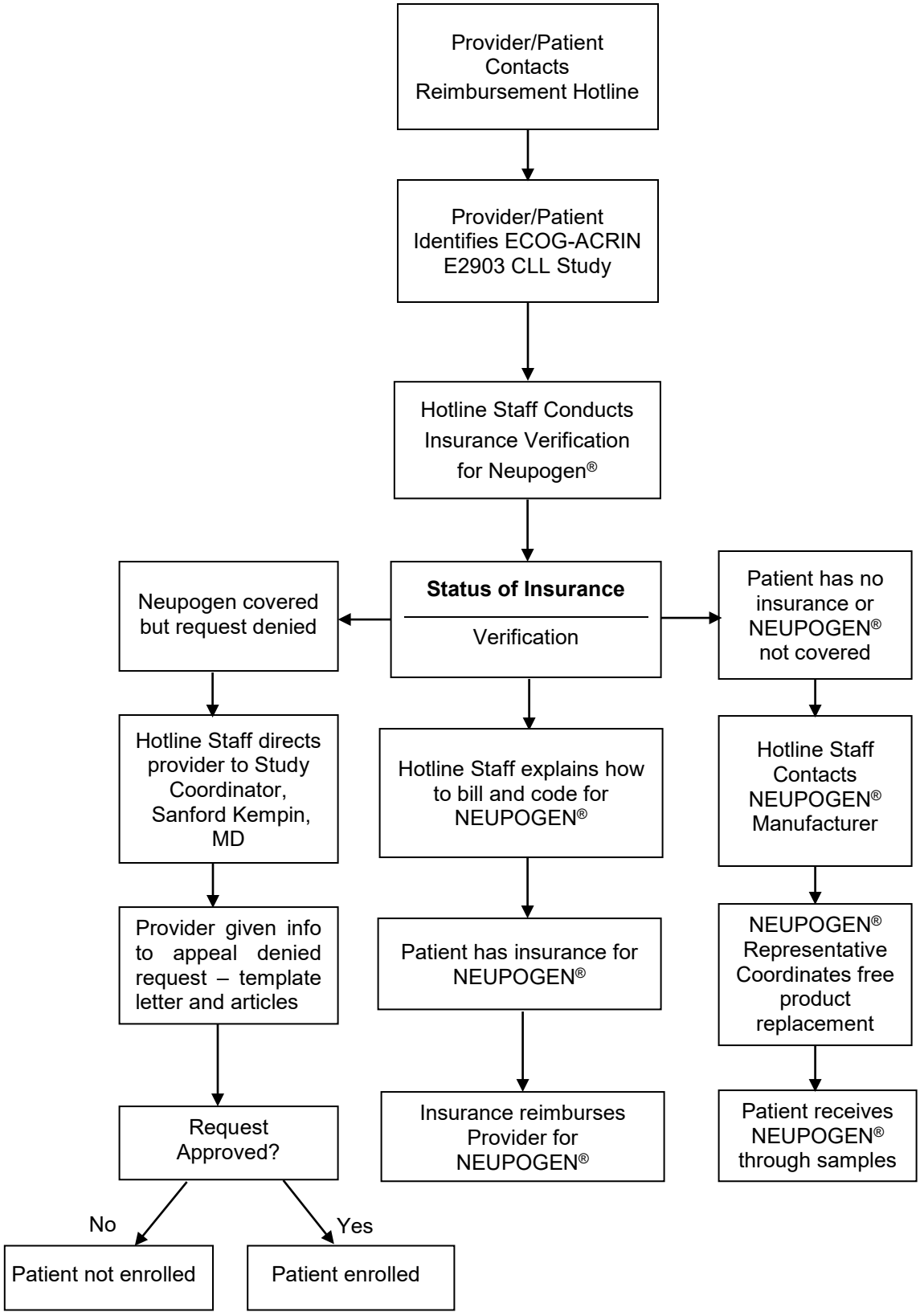
Reimbursement Hotline: 1-800-272-9376

Hours: Monday through Friday 9:00 AM – 5:00 PM ET

Contact: Amgen Claims Specialist – Jeanne Pettit

When calling be prepared with the following information:

1. Identify yourself as being with the ECOG-ACRIN CLL Trial E2903.
2. Name and address of physician.
3. Date of service.
4. Patient name and ECOG-ACRIN Patient Sequence Number.
5. Name and address of the insurer.
6. Insurer's reason for rejection claim.
7. Copy of the claim.


Provider/Patient Contacts Reimbursement Hotline
Provider/Patient Identifies ECOG-ACRIN E2903 CLL Study
Hotline Staff Conducts Insurance Verification for Neupogen®
Status of Insurance Verification
Neupogen covered but request denied
Patient has no insurance or NEUPOGEN® not covered
Hotline Staff directs provider to Study Coordinator, Sanford Kempin, MD
Hotline Staff explains how to bill and code for NEUPOGEN®
Hotline Staff Contacts NEUPOGEN® Manufacturer
Provider given info to appeal denied request – template letter and articles
Patient has insurance for NEUPOGEN®
NEUPOGEN® Representative Coordinates free product replacement
Request Approved?
Insurance reimburses Provider for NEUPOGEN®
Patient receives NEUPOGEN® through samples
No
Yes
Patient not enrolled
Patient enrolled

NEUPOGEN® SAMPLE REQUEST

Date Submitted: _____

Requesting Physician:

Name: _____ Prof. Designation: _____

Mailing/Shipping Address:

_____

_____

Telephone: _____ FAX: _____

Hospital/Office/Clinic:

Name:_____

Contact Person: _____Title:_____

Shipping Address: _____

_____

Telephone: _____FAX:_____

DEA#: _____Expiration Date: _____
(Number and Photocopy Required)

REQUEST AND CERTIFICATION

I hereby request that AMGEN furnish me with _____ boxes NDC# _____ at the mailing/shipping address listed on this form. I understand and agree that free sample units furnished in response to this request will only be used in furtherance of the above mentioned trial and are not to be sold, purchased, or traded. I certify that no charge for any such units used in the treatment of any patient will be made, and no bill for or containing any such charge will be submitted to the patient or any third party.

Physician Signature: _____Date: _____

Physician address (if different from above):

Understood and agreed to on behalf of hospital/office/clinic by:

Name: _____ Title: _____ Date: _____

Telephone: _____

for AMGEN Use Only

Project Manager: Terry M. Cook Phone No: _____ Patient ID#: _____

cc: Jeanne Petit, Robert A. Butler

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Appendix IV

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at **http://www.ecog.org**. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important clinical program. Programs like this offer a chance to get the best care while helping us make better care available for all patients. Many questions remain unanswered in cancer. With the help of people like you who participate in these programs, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe this program will provide you with high quality, thorough care. Your physicians and research staff will maintain very close contact with you. This is important to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of [INSTITUTION] and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Appendix V

Grading Scale for Hematologic Toxicity in CLL Studies

Grading Scale for Hematologic Toxicity in CLL Studies[1]

Decrease from Pretreatment value (%)	Grade[2] Platelets[3]	Grade[2] Hemoglobin[4]
No change – 10%	0	0
11-24%	1	1
25-49%	2	2
50-74%	3	3
≥ 75%	4	4

1. A decrease in circulating granulocytes is not being considered since it is not a reliable index in CLL.
2. Grades: 1-mild; 2-moderate; 3-severe; 4-life-threatening. Grade 5 (fatal) toxicity can potentially occur at any level of decrease from pretreatment values and will be recorded as such.
3. If, at any level of decrease the platelet count is ≤ 20,000/μL, this will be considered grade 4, unless the initial platelet count was ≤ 20,000/μL in which case the patient is inevaluable for toxicity referable to platelet counts.
4. Baseline and subsequent hemoglobin determinations must be immediately prior to any given transfusions.

*Cheson BD, et al: National Cancer Institute-sponsored working group guidelines for chronic lymphocytic leukemia: Revised guidelines for diagnosis and treatment. Blood 87:4990-4997, 1996.

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Appendix VI

Rai Staging System for CLL

Rai Staging System for CLL (5)

Stage 0	Lymphocytosis in blood shown to be monoclonal by immunophenotyping or molecular techniques and a morphology consistent with CLL.
Stage 1	Same as Stage 0 with lymphadenopathy.
Stage 2	Same lymphocytosis as Stage 0 plus enlarged spleen and/or liver.
Stage 3	Includes lymphocytosis and anemia defined as Hgb ≤ 11 gm/dL or Hct ≤ 33%.Physical findings of lymphadenopathy, hepato- or splenomegaly are not required.
Stage 4	Includes the findings at diagnosis of lymphocytosis as defined in Stage 0, with thrombocytopenia ≤ 100,000/μL.

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Appendix VII

Treatment Evaluation

	CR[1]	NPR[2]	PR[3]	PROG
PHYSICAL EXAM				
Nodes	None	None	50% ↓	50% ↑, new nodes
Liver/spleen	Not palpable	Not palpable	50% ↓	50% ↑, newly palpable
Symptoms	None	None	N/A	N/A
PERIPHERAL BLOOD				
ANC	1,500/μL	1,500/μL	1,500/μL or 50% improvement from baseline	
Platelets	>100,000/μL	>100,000/μL	>100,000/μL or >50% improvement from baseline	
Hemoglobin	>11.0 g/dL without transfusion	>11.0 g/dL without transfusion	>11.0 g/dL or >50% improvement from baseline without transfusion	
Lymphocytes	4,000/μL	4,000/μL	50% ↓	≥ 50% ↑ to at least 5,000/μL
BONE MARROW	≤ 30% lymphocytes; No nodules	Bone marrow nodules	N/A	N/A

1. Complete remission (CR) requires fulfillment of all physical exam and peripheral blood criteria for a duration of > 2 months. A bone marrow aspirate and biopsy are required to document the response as a complete (≤ 30% lymphocytes with no nodules).
2. Nodular partial remission (NPR) is essentially a patient in who it appeared that CR had been obtained but nodules are present in the bone marrow. It requires fulfillment of all physical exam and peripheral blood criteria for CR; however, when the bone marrow is done to confirm CR, nodules of malignant lymphocytes are found.
3. Partial remission (PR) requires fulfillment of the above noted decrease in circulating lymphocytes, regression in adenopathy and/or hepatosplenomegaly, and one other parameter listed above for a duration of > 2 months.

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Appendix VIII

Specimen Kit: Packaging and Shipping Instructions

***PLEASE AVOID DRAWING OR SHIPPING SPECIMENS ON FRIDAYS OR PRIOR TO HOLIDAYS**

1. Complete Patient Information Form (See Appendix IX Page 2)

Send CBC and Differential Information (WBC and % Lymphocytes essential)
Specimen Checklist:

_____ Peripheral Blood - 10 - 10cc Heparin Tubes (Green top) @ Baseline
5 - 10cc Heparin Tubes (Green top) after Baseline

_____ Peripheral Blood - 1 -10cc Red top tube for serum

Rev. 1/09 _____ Bone Marrow Block or 8-10 unstained positively charged Slides (Shipped separately)

Label all tubes with the Patient's Initials and ID#

Place filled tubes in styrofoam container with absorbent material and put in corrugated mailer box

Place Patient Information Form into the mailing box

Fill out provided Federal Express Mail Form for No Charge Billing including your name, telephone number, address, and date on the left side of the airbill

Specimens are shipped at ROOM TEMPERATURE

Rev. 7/07 Notify Jenn Abrahamson or Charla Secreto (507-284-3805) at the Mayo Clinic that samples are being sent overnight priority delivery.

SPECIMENS MUST BE MAILED THE SAME DAY AS COLLECTED

SHIP SPECIMENS TO:

Rev. 1/09
Rev. 7/07

Charla Secreto
Mayo Clinic
613 Stabile
200 First Street SW
Rochester, MN 55905

Phase II Trial of Pentostatin, Cyclophosphamide and Rituximab (PCR) Followed By Campath-1H For Previously Treated Relapsed or Refractory Patients With Chronic Lymphocytic Leukemia

Appendix IX

Specimen Kit: Patient Information Form

PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND PRE-HOLIDAYS

Specimen Date: _____ Time Drawn: _____

Institution/Affiliate: _____

Physician:

_____

Patient Name:

_____

Hospital I.D. or Social Security #: _____

ECOG-ACRIN Protocol #: E2903

ECOG-ACRIN Sequence #: _____

Contact /Coordinating Person:

Name: _____

Institution: _____

Address: _____

City: _____

Phone #: _____

PLEASE INCLUDE A CURRENT WHITE BLOOD COUNT AND DIFFERENTIAL:

WBC _____

LYMPHOCYTE % _____

Study Time Point (circle one):

1. Baseline
6. Months
8. Months
10. Months
12. Months
18. Months
7. 2 Year
8. 2-5 Year follow up
9. Other _____

Any questions concerning these samples or to obtain an E2903 Specimen Kit, please contact:

Rev. 7/07
Rev. 1/09

Charla Secreto
Hematology Research
Tel: (507) 284-3805

* Affiliates who anticipate participating in this study should please call in advance for kits